

4-Unsubstituted, 5-Amino and 5-Unsubstituted, 4-Aminoimidazoles

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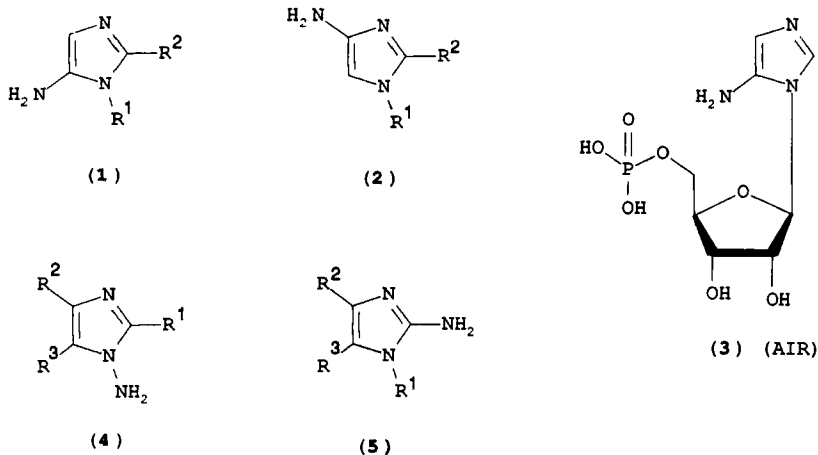
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I. Introduction

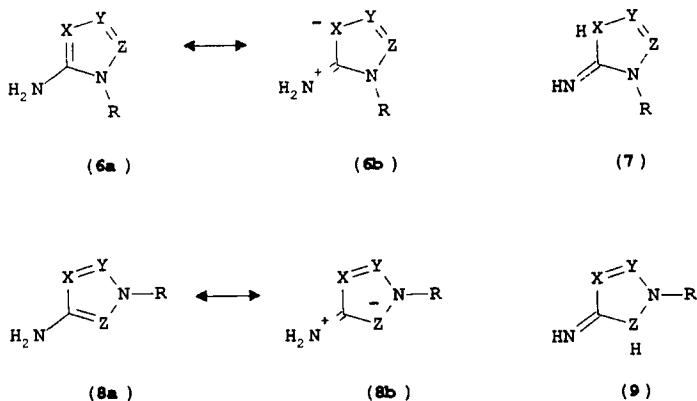
The purpose of this review is to survey the chemistry of amines having the general structure (1) and (2). The literature available to the authors up to June 1993 has been covered. Earlier reviews [53HC(1)141; 57HC223; 67CRV533; 70AHC(12)181, 70JPS1533; 80AHC(27)320; 84MI2; 86MI2; 86MI3] covering the chemistry of aminoimidazoles have been dominated by derivatives in which an electron-withdrawing substituent on the imidazole ring stabilizes the amine. The literature on such molecules is extensive and is not included here. Similarly, 1-aminoimidazoles (4) and the more familiar 2-aminoimidazoles (5) are also excluded from our survey, although leading references are given in Section II as an aid to the reader. A feature of special interest in the imidazoles to be discussed in this review is the absence of a substituent on the ring carbon atom adjacent to the amino substituent. These structures (1 and 2) are associated with properties which are of chemical, biochemical, and synthetic interest.

In most living systems, 5-amino-1-(β -D-ribofuranosyl)-imidazole-5'-monophosphate (3) (AIR) is an intermediate in the *de novo* biosynthesis of purine ribonucleotides (57JBC1005; 59BBA367, 59JBC1799; 64SCI1056; 72MI1, 72MI2; 86B4356; 86B4366; 88MI1). It is also a biosynthetic precursor of thiamin in some lower organisms (83MI3; 84JA3857; 86BBR1136,



86M11). Although Mother Nature has been utilizing this important aminoimidazole derivative (3) as a synthetic intermediate for millions of years, the chemistry of simple 5-aminoimidazoles (1) and the isomeric 4-aminoimidazoles (2) has received relatively little attention from chemists. One reason for this apparent underachievement is the low stability of these heterocyclic amines. However, recent studies have demonstrated that simple derivatives can be isolated and characterized or alternatively generated *in situ* in good yield and used without isolation [89CC551; 92JCS(P1)2779, 92JCS(P1)2789].

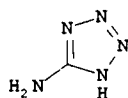
The stabilities and reactivities of monoaminoazoles (6 and 8) vary considerably and are related to the number of nitrogen atoms in the heterocyclic ring. Physical evidence indicates that members of this family exist as primary amines (6 and 8) rather than as imino tautomers (7 and 9). Nitrogen



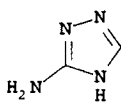
In the generalized formulae (6-9), X, Y, and Z represent substituted carbon (CR) or nitrogen (N) atoms.

atoms stabilize dipolar canonical forms (e.g., **6b** and **8b**), which contribute significantly to the electronic structure.

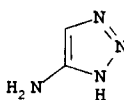
Structures (**10–18**) show the nine fundamental monoaminoazoles. 5-Aminotetrazole (**10**) (84MI3), which is usually obtained as a monohydrate (mp 203°C) but which can be obtained in anhydrous form, is a stable crystalline compound and has been widely employed to make tetrazole derivatives with potentially interesting biological properties (77AHC323; 80MI1). Similarly, 3-amino-1,2,4-triazole (**11**) (mp 152–156°C) (55OSC95) and 4-amino-1,2,3-triazole (**12**) (mp 74–75°C) (73TL1137) have been isolated as stable, crystalline, free bases. In contrast, very little is known about simple aminopyrroles but they are highly reactive, unstable species: the parent systems (**17** and **18**) have not been isolated. Systems associated with two nitrogen atoms in the azole ring, namely aminopyrazoles (e.g., **13** and **14**) and aminoimidazoles (e.g., **15** and **16**) enjoy intermediate stability and reactivity. 3-Aminopyrazole (**13**) (mp 37–39°C) (73OSC39) and 4-



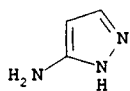
(**10**)



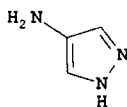
(**11**)



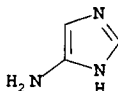
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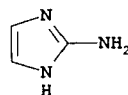
(**13**)



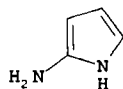
(**14**)



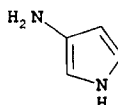
(**15**)



(**16**)



(**17**)



(**18**)

aminopyrazole (**14**) (mp 81°C) (84MI1) have been characterized but, so far, the parent aminoimidazoles (**15** and **16**) have evaded isolation as the free base, although they have been isolated as simple salts (41MI1; 19JCS217; 56JCS307).

In this review, we are concerned with simple derivatives of the amine (**15**). These are sufficiently stable to be accessible but reactive enough to be useful synthetic intermediates.

II. 1-Aminoimidazoles and 2-Aminoimidazoles: A Synopsis

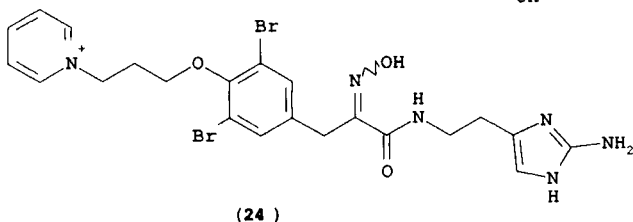
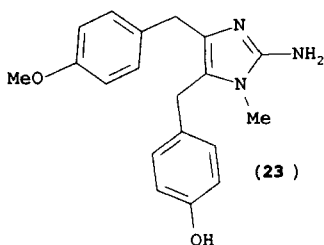
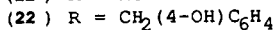
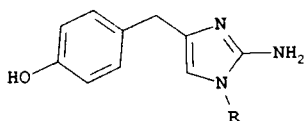
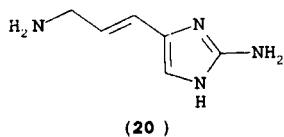
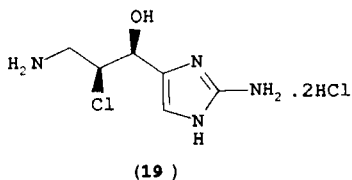
A. 1-AMINOIMIDAZOLES

An up-to-date summary of this class of aminoimidazoles (**4**) is contained in a recent review [92AHC(53)85]. The parent molecule (**4**; $R^1 = R^2 = R^3 = H$) is unstable and has been isolated only as its hydrochloride salt (82S592). A number of substituted derivatives have been described, but studies of this class of heterocyclic amine remain limited.

B. 2-AMINOIMIDAZOLES

The 2-aminoimidazoles (**5**) are well-described compounds and have received considerable attention [19JCS217; 53HC(1)141; 56JCS307; 57HC223; 62JOC886; 64JOC3118; 78JOC4784; 80AHC(27)320; 84MI2; 86MI3], especially since the discovery of the 2-nitroimidazole antibiotics related to azomycin for which the 2-aminoimidazoles became key intermediates (65JA389). Recent interest has been stimulated by the discovery of the natural product Girolline (**19**), which was isolated from a marine sponge and shown to possess potent anticancer properties (89MI1). Syntheses that provided compound (**19**) as a racemate were rapidly developed (89T6713; 90TL3871; 91TL1419) and recent improvements have produced an enantioselective synthesis (91TL4905; 92T4327). A possible biosynthetic precursor is the aminopropene derivative (**20**), which was also isolated from marine sponges (91MI2). Numerous other diverse 2-aminoimidazoles have been isolated from this biological source, such as the substituted benzyl derivatives (**21–23**) (89T2193; 91MI1) and the pyridine containing alkaloid (**24**) (92TL2597); others have been reported (73CC78; 85JOC4163, 85TL4517).

2-Aminoimidazole (**16**) has also been identified as a metabolite from marine sponges (74MI1) and has been implicated as an *in vivo* progenitor of a class of marine pigments (92TL4385).

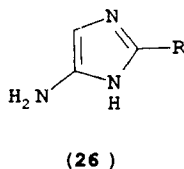
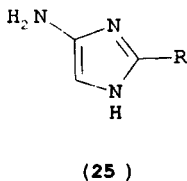


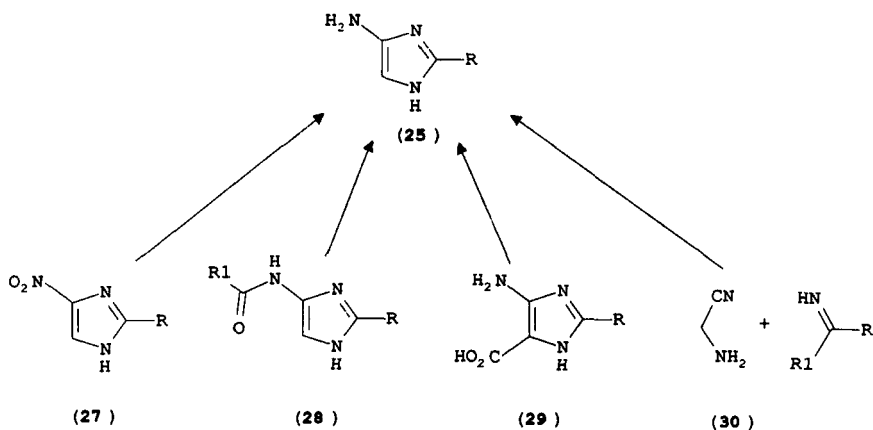
III. 5(4)-Unsubstituted, 4(5)-Aminoimidazoles

The opportunity to tautomerize endows the 4(5)-aminoimidazoles ($25 \rightleftharpoons 26$) with some unique properties and it is appropriate to discuss them separately.

A. SYNTHESIS

Four approaches to the synthesis of 4(5)-aminoimidazoles (**25**) have been described and are summarized in Scheme 1. These are (a) reduction of 4(5)-nitroimidazoles (**27**), (b) hydrolysis of carbamates and amides (**28**),





SCHEME 1

(c) decarboxylation of imidazole carboxylic acids (29), and (d) cyclization of nitrile derivatives prepared from aminoacetonitrile (30).

1. Reduction of 4(5)-Nitroimidazoles

Prior to work by Hunter and Hlynka (37BJ488), all attempts to obtain 4(5)-aminoimidazoles (25) by reduction of the corresponding nitroimidazoles (27) using a variety of reducing agents resulted in failure. For example, treatment of 4(5)-nitroimidazole (27; R = H) with tin(II) chloride in hydrochloric acid gave only ammonia and glycine (19JCS217; 20JCS668). Other reducing reagents that were investigated without success (30JCS268) included (a) iron in either aqueous acetic acid or ethanolic hydrochloric acid, (b) ferrous sulfate and aqueous alkali, (c) activated aluminum, and (d) sodium sulfide.

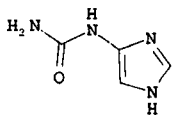
In 1937 Hunter and Hlynka were able to reduce a methanolic solution of 4(5)-nitroimidazole (27; R = H) with sodium amalgam and trap the 4(5)-aminoimidazole (25; R = H) with cyanic acid giving the urea derivative (31) (37BJ488). Other reducing agents gave inferior results. Subsequently, 4(5)-aminoimidazole (25; R = H) was obtained as either its dihydrochloride (30%) or dipicrate salt but the isolation procedures were lengthy and difficult (41MI1).

The use of powdered zinc in hydrochloric acid has been reported to reduce 4(5)-nitroimidazole (27; R = H) to 4(5)-aminoimidazole (25; R = H), but the yield was not recorded [56JBC(223)985]. In another study, treatment of 4(5)-nitroimidazole (27; R = H) with zinc dust in tetrafluoroboric acid solution followed by *in situ* diazotization of the amine (25; R = H), which was presumed to be formed, gave 4-fluoroimidazole (17%) (73JA4619, 73JOC3647).

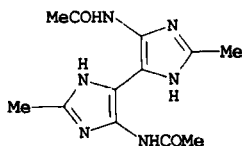
Raney nickel reduction of 4(5)-nitroimidazole (**27**; R = H) in a mixture of acetic anhydride and acetic acid gave a diacetylated compound (35%) that was identified as 1- (or 3-) acetyl-4-acetamidoimidazole (57JA2188).

The most convenient method of generating 4(5)-aminoimidazoles (**25**) has been found to be by catalytic hydrogenation using Pd/C catalyst. Reduction of 4(5)-nitroimidazole (**27**; R = H) in aqueous monopotassium dihydrogen phosphate solution using 5% Pd/C catalyst was reported [56JBC(218)175; 61MI1] to give a stable solution of the amine (**25**; R = H), although earlier workers (41MI1) had claimed that the amine (**25**; R = H) was very unstable in aqueous solution. Subsequently, this method was used to generate and trap 4(5)-aminoimidazole (**25**; R = H) with 1,1,3,3-tetramethoxypropane to give imidazo[1,5-*a*]pyrimidine (see Section III,B,5) (72BSF2481). More recently, dioxane has been found to be an excellent solvent for catalytic reduction of 4(5)-nitroimidazoles (**27**): the reduction can often be carried out in the presence of a trapping agent [92JCS(P1)2779]. Using this method, 4(5)-aminoimidazole (**25**; R = H) has been reacted with a number of electrophilic reagents to give good yields of synthetically useful *N*-adducts, which have been used to generate a variety of novel heterocyclic products [92JCS(P1)2779, 92JCS(P1)2789]. These transformations of 4(5)-aminoimidazole (**25**; R = H) are discussed in Section III,B,5.

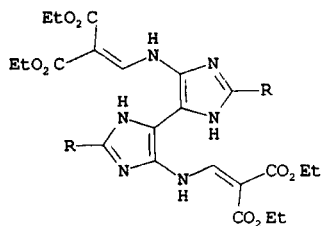
An unexpected reaction occurs when 2-alkyl-4(5)-nitroimidazoles (**27**; R = alkyl) are reduced in protic solvents [92JCS(P1)2779]. Catalytic hydrogenation of 2-methyl-4(5)-nitroimidazole (**27**; R = Me) in a solution of acetic anhydride and acetic acid gave 4,4'-diacetamido-2,2'-dimethyl-5,5'-diimidazole (**32**; yield 10%) in addition to the expected 4-acetamido-1-acetyl-2-methylimidazole (28%). Similarly, reduction of the 2-alkyl-4(5)-nitroimidazoles (**27**; R = Me, Et, *i*Pr) in ethanol solution in the presence of diethyl ethoxymethylenemalonate [EMME; (**135**)] gives predominantly the 5,5'-diimidazole adducts (**33**). The formation of these products (**33**) is believed to involve an electrophilic addition of the starting material (**27**) to the electron-rich aminoimidazoles (**25**) [92JCS(P1)2779]. Interestingly, replacement of ethanol by dioxane suppressed diimidazole formation.



(31)



(32)



(33)

A high yielding method of synthesis of amino compounds from both aliphatic and aromatic nitro compounds was applied to 2-methyl-4(5)-nitroimidazole (**27**; R=Me), but with only limited success (84TL3415). The method used ammonium formate as a catalytic hydrogen transfer agent with 10% Pd/C in dry methanol but the authors noted only partial reduction with rapid decomposition of the resulting product, presumed to be the amine (**25**, R=Me). In contrast, the use of formic acid as the hydrogen transfer agent has been reported to be a useful method [77JCS(P1)443]. Thus, 2-methyl-4(5)-nitroimidazole (**27**; R=Me) was reduced to the corresponding amine (**25**; R=Me) in formic acid solution with Pd/C as catalyst, but the yield and method of isolation were not recorded.

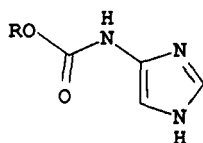
The electrolytic reduction of 4(5)-nitroimidazole (**27**; R=H) has been shown (83MI1) to proceed readily in a six-electron process but this method has been used only to determine the electronic requirements for the reduction and not for synthetic purposes.

Gamma-ray-induced reduction of both 4(5)-nitroimidazole (**27**; R=H) and 2-methyl-4(5)-nitroimidazole (**27**; R=H) in aqueous sodium formate or isopropanol solutions has been studied (83MI2) at neutral pH under inert conditions. Both compounds (**27**; R=H, Me) were reduced stepwise with the consumption of six electrons.

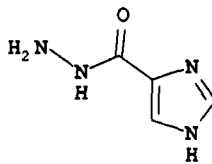
2. Hydrolysis of Carbamates and Amides

Early attempts to prepare 4(5)-aminoimidazole (**25**; R=H) from the carbamates (**34**; R=Me, Et) [obtained from the hydrazide (**35**) using the Curtius method] by either acid- or base-catalyzed hydrolysis resulted in failure (30JCS268).

However, in a later study, Cohen and Kirk described a successful hydrolysis of the *t*-butyl derivative (**34**; R=*t*Bu) using tetrafluoroboric acid (73JA4619, 73JOC3647). The resulting 4(5)-aminoimidazole (**25**; R=H) was diazotized *in situ*, and the solution irradiated to give 4-fluoroimidazole (yield 41%). This carbamate (**34**; R=*t*Bu) was also hy-



(**34**)



(**35**)

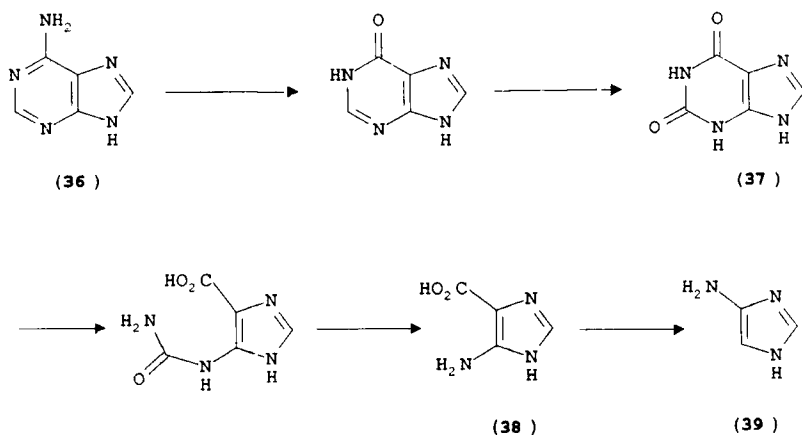
dolyzed by concentrated hydrochloric acid to give 4(5)-aminoimidazole (**25**; R = H) as the dihydrochloride salt (87JOC5538).

Hunter and Nelson (41MI1) attempted the preparation of 4(5)-aminoimidazole (**25**; R = H) from its acetyl derivative (**28**; R = H, R¹ = Me), which they obtained by reduction of 4(5)-nitroimidazole (**27**; R = H) with tin(II) chloride in acetic anhydride. The authors noted that hydrolysis of compound (**28**; R = H, R¹ = Me) with aqueous acids resulted in fission of the imidazole ring and formation of acetic acid, formic acid, ammonia, and glycine. Base hydrolysis gave similar results (41MI1), although a trace of 4(5)-aminoimidazole (**25**; R = H) was detected.

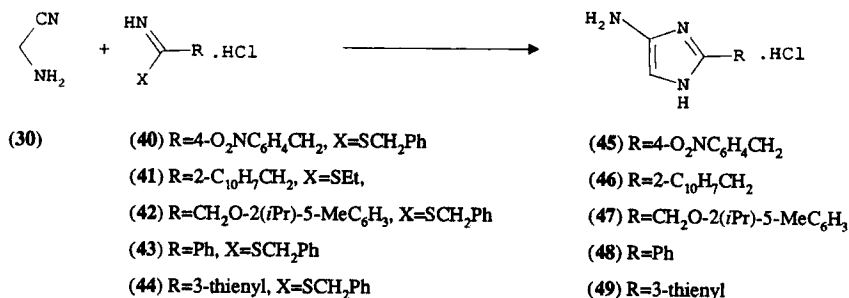
3. Decarboxylation of Imidazole Carboxylic Acids

Cell-free extracts of *Clostridium cylindrosporum* and *Clostridium purinolyticum* have been shown [56JBC(222)537; 61MI1; 82MI2] to produce 4(5)-aminoimidazole (**39**) by decarboxylation of 4-amino-5-imidazole carboxylic acid (**38**) during the degradation of adenine (**36**) via xanthine (**37**) (Scheme 2). A similar mode of degradation to give 4(5)-aminoimidazole (**39**) was demonstrated [56JBC(218)175] during the enzymatic degradation of xanthine (**37**) by *Clostridium cylindrosporum*. The products of degradation were identified by comparison of chromatographic behavior and spectral properties with those obtained via a synthetic route [56JBC(218)175].

4-Amino-5-imidazole carboxylic acid (**38**) has been synthesized from 4-nitro-5-imidazole carboxylic acid by catalytic hydrogenation and shown [56JBC(218)175] to spontaneously decarboxylate at low pH to give 4-aminoimidazole (**39**).



SCHEME 2



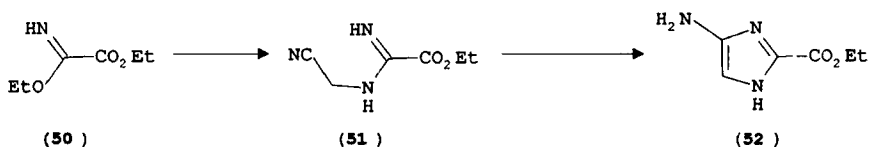
SCHEME 3

4. Cyclization of Nitrile Derivatives

The 4(5)-amino-2-substituted imidazoles (**45**) and (**46**) have been prepared (50JCS2775) by condensation of aminoacetonitrile (**30**) with the thioiminoether hydrochloride salts (**40**) and (**41**), respectively. These 4(5)-aminoimidazoles (**45**, **46**) were isolated as their hydrochloride salts in yields of 36 and 90% (Scheme 3).

This approach (Scheme 3) has been applied (53JCS1636) to the synthesis of 4(5)-aminoimidazole derivatives with potential antihistamine or anthelmintic properties. For example, 4(5)-amino-2-thymyloxymethylimidazole (**47**) was obtained from benzyl-thymyloxy acetothioimide hydrochloride (**42**) (75%). Similarly, 4(5)-amino-2-phenylimidazole (**48**) and 4(5)-amino-2-(thiophen-3-yl)imidazole (**49**) were prepared (72CA19645) from benzyl-phenyl acetothioimide hydrochloride (**43**) and benzyl-(thiophen-3-yl) acetothioimide hydrochloride (**44**), respectively.

Recently, ethyl carboethoxyformimidate (**50**) has been shown (82TL3357; 86T2625) to be a versatile synthetic reagent in nitrogen heterocyclic chemistry. An ethereal solution of the reagent (**50**) on condensation with aminoacetonitrile (**30**) gave the intermediate (**51**), which upon heating in ethanolic solution gave the 4(5)-aminoimidazole (**52**) (91%) as the hydrobromide salt (Scheme 4).

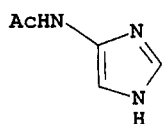


SCHEME 4

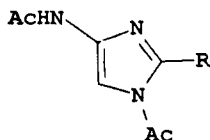
B. CHEMICAL PROPERTIES

1. Acylation

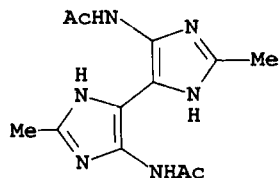
The reduction of 4(5)-nitroimidazole (**27**; R = H) in the presence of acetic anhydride by either stannous chloride (41MI1) or catalytic hydrogenation (Pd/C as catalyst) [92JCS(P1)2779] gave the acetamido derivative (**53**). When Raney nickel was used as reducing agent, a diacetylated product was obtained (57JA2188) and, although its structure (**54**; R = H) was not proven, hydrolysis produced the acetamide (**53**; yield 88%). The catalytic hydrogenation of 2-methyl-4(5)-nitroimidazole (**27**; R = Me) in the presence of acetic anhydride gave a mixture of two products, which were identified as the diacetylated product (**54**; R = Me) and the diimidazole (**32**) [92JCS(P1)2779].



(53)



(54)

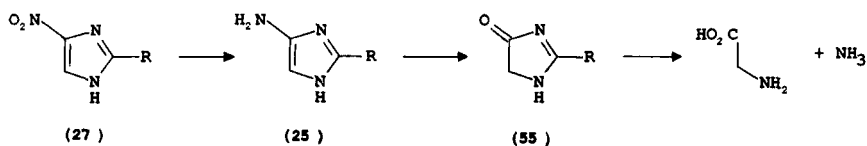


(32)

2. Diazotization

Diazotization provided the first evidence (30JCS268) that 4(5)-aminoimidazoles (**25**) could be regarded as aromatic amines. It was shown (20JCS668; 50JCS2775) that red coloration resulted from the treatment of diazotized 4-aminoimidazoles with sodium β -naphthoxide (20JCS668; 22JCS2616; 50JCS2775). Diazotization was used as a means of assessing the progress of the reduction of 4(5)-nitroimidazole (**27**; R = H) by sodium amalgam (41MI1). Early work [56JBC(218)175] reported that a blue coloration was produced by diazotized 4(5)-aminoimidazole (**25**; R = H) in the Pauly test, but later workers [56JBC(218)189] failed to repeat this reaction.

4(5)-Aminoimidazole (**25**; R = H), which was generated *in situ* either by reduction of 4(5)-nitroimidazole (**27**; R = H) (Section III,A,1) or by hydrolysis of *t*-butyl-imidazole-4-carbamate (Section III,A,2) was diazotized *in situ* in tetrafluoroboric acid to give 4-fluoroimidazole (73JA4619, 73JOC3647). Diazotization was also successfully performed on the dihydrochloride salt of 4(5)-aminoimidazole (**25**; R = H) (87JOC5538).



SCHEME 5

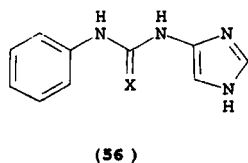
3. Hydrolysis

Early attempts (19JCS217) to obtain 4(5)-aminoimidazoles (**25**) by chemical reduction of appropriate nitro precursors resulted in ring fission, with two of the three nitrogen atoms being converted to ammonia. Subsequent work indicated the mode of fission (20JCS668). When 4-nitroimidazole (**27**; R = H) was reduced in cold hydrochloric acid containing just sufficient stannous chloride to effect reduction, the 4(5)-aminoimidazole (**25**; R = H) formed was rapidly hydrolyzed to 4-imidazolone (**55**; R = H), which underwent fission to give glycine and ammonia (Scheme 5). In a similar procedure (20JCS668), glycine, acetamidine, and ammonia were obtained by chemical reduction of 2-methyl-4(5)-nitroimidazole (**27**; R = Me).

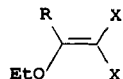
4. Addition Reactions

Early studies on 4(5)-aminoimidazole (**25**; R = H) gave a stable urea derivative (37BJ488). Thus, treatment of a solution of 4(5)-aminoimidazole (**25**; R = H), made slightly acidic by addition of acetic acid, with potassium cyanate gave *N*-imidazol-4-yl-urea (**31**) (8%). *N*-Imidazol-4-yl-urea (**31**) was similarly obtained using the dihydrochloride salt of 4(5)-aminoimidazole (**25**; R = H) (41MI1).

An improved procedure for preparing urea derivatives involves reaction of isocyanates or isothiocyanates with 4(5)-aminoimidazole (**25**; R = H) in tetrahydrofuran solution [92JCS(P1)2779]. A THF solution of 4(5)-aminoimidazole (**25**; R = H) generated *in situ* and then treated with the appropriate reagent gave either *N*-imidazole-4-yl-*N'*-phenylurea (**56**; X = O) (32%) or *N*-imidazol-4-yl-*N'*-phenylthiourea (**56**; X = S) (21%).



- (57) Y = OMe, X = CN
 (58) Y = OEt, X = CN
 (59) Y = SMe, X = CN
 (60) Y = OEt, X = CO₂Et



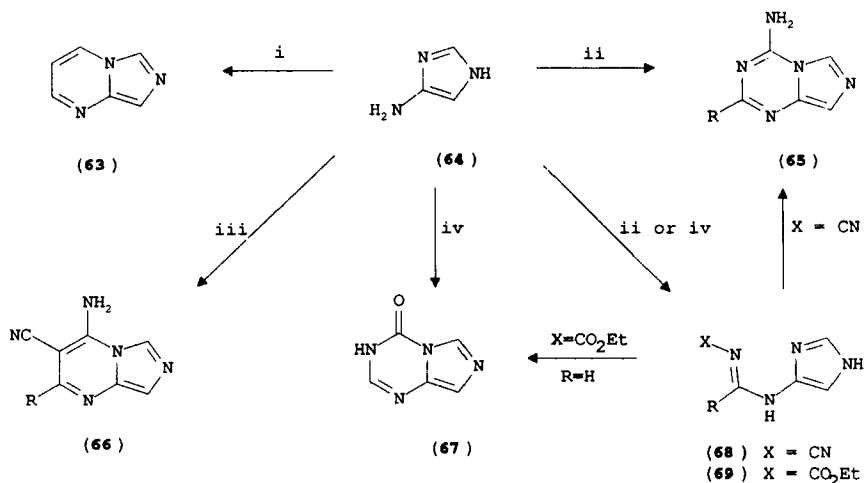
- (61) X = CN
 (62) X = CO₂Et

5. Addition-Elimination Reactions

4(5)-Aminoimidazole (**64**) has been reported to react with various bifunctional reagents to give bicyclic systems (Scheme 6). In some cases the initial *N*-addition-elimination product has been isolated (e.g., **68** and **69**).

When a solution of 4(5)-aminoimidazole (**64**) (Scheme 6) in dipotassium monohydrogen phosphate solution was treated with 1,1,3,3-tetramethoxypropane, imidazo[1,5-*a*] pyrimidine (**63**) was obtained as a yellow hygroscopic solid (40%) [71BSF(2)1031].

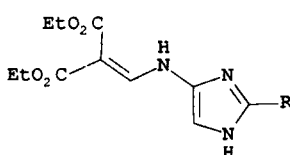
Dioxane solutions of 4(5)-aminoimidazole (**64**) have been treated with several reagents [92JCS(P1)2789]. Imidazo[1,5-*a*]-1,3,5-triazines (**65**; R=Ph, Me SMe) were obtained by reaction with methyl *N*-cyanobenzimidate (**57**; R = Ph), ethyl *N*-cyanoacetimidate (**58**; R = Me), and dimethyl *N*-cyanodithioiminocarbonate (**59**; R = SMe). The uncyclized product (**68**; R = H) (73%), obtained by condensation with ethyl *N*-cyanoformimidate (**58**; R = H), underwent facile cyclization to give the imidazo[1,5-*a*]-1,3,5-triazine (**65**; R = H). Likewise, the condensation adduct (**69**; R = H) (78%) was obtained using ethoxy methyleneurethane (**60**; R = H) and this underwent base-catalyzed cyclization to give the imidazo[1,5-*a*]-1,3,5-triazinone (**67**). Imidazo[1,5-*a*]pyrimidines (**66**; R = H, Me) were obtained from the condensation of 4(5)-aminoimidazole



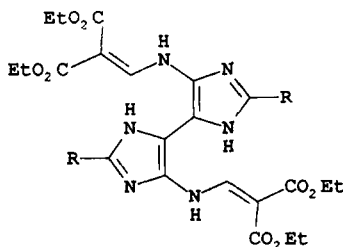
SCHEME 6

(64) with ethoxy methylenemalononitriles (**61**; R = H, Me) [92JCS(P1)-2789].

An unusual observation was noted when ethanolic solutions of 2-alkyl-4(5)-aminoimidazoles (**25**; R = alkyl) were allowed to react with diethyl ethoxymethylenemalonate (**62**; R = H) [92JCS(P1)2789]. In addition to anticipated products (**70**), which were obtained in low yield ($\leq 10\%$), the diimidazole derivatives (**33**; R = alkyl) were formed in ca.30% yield. The mechanism of formation of the diimidazole products (**33**) has been interpreted in terms of a reaction between the aminoimidazole (**25**) and its nitroimidazole precursor (**27**) during the reduction process. In particular, a soft-soft interaction between the highest occupied molecular orbital (HOMO) of the aminoimidazole (**25**) and the lowest unoccupied molecular orbital (LUMO) of the nitroimidazole (**27**) is favorable and probably leads to an intermediate, which on tautomerism, elimination of water, and further reduction, gives the observed products (**33**). The reactions of aminoimidazoles with hard and soft electrophiles is further discussed in Section VI,C.



(70)



(33)

A key requirement for diimidazole formation appears to be substitution of the 2-position, since 4(5)-aminoimidazole (**25**; R = H) gave only the monomeric species (**70**; R = H). The choice of solvent is also important: when dioxane replaced ethanol as solvent, diimidazole formation was suppressed [92JCS(P1)2789].

6. Miscellaneous Reactions

During a study of urinary metabolites, the color reactions of 4(5)-aminoimidazole (**25**; R = H) with various reagents was investigated. The results are summarized in Table I (65MI1).

With a solution of ninhydrin in pyridine, 4(5)-aminoimidazole (**25**; R = H) gave a grass-green color, and with ferric chloride solution in acetic acid a purple coloration was observed. Acidic solutions of bromine and potassium permanganate were decolorized by 4(5)-aminoimidazole (**25**;

TABLE I
COLOR REACTIONS OF 4(5)-AMINOIMIDAZOLE (25; R = H) WITH SPRAY REAGENTS

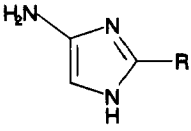
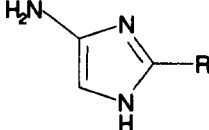
<div style="text-align: center;">  <p>(25)</p> </div>	
Reagent	Color
Diazotized sulphanilic acid	Blue
Diazotized 4-nitroaniline	Gray-blue
4-Dimethylaminobenzaldehyde in ethanolic HCl (Ehrlich's reagent)	Orange
Ammoniacal silver nitrate	Gray
Nitrous acid plus coupling component (Bratton-Marshall)	Gray
Ninhydrin	Mauve
Mercury-diphenyl carbazone	Gray
Anisidine	Purple

TABLE II
KNOWN 4(5)-AMINOIMIDAZOLE DERIVATIVES (25)

<div style="text-align: center;">  <p>(25)</p> </div>				
R	Free base	Salt	<i>In situ</i>	Reference
H	—	2HCl	—	41MI1; 87JOC5538
H	—	—	✓	56JBC(218)175, 56JBC(223)985; 57JA2188; 72BSF2481; 73JA4619; 92JCS(P1)2779
Me	—	—	✓	92JCS(P1)2779
Et	—	—	✓	92JCS(P1)2779
<i>i</i> Pr	—	—	✓	92JCS(P1)2779
Ph	—	HCl	—	72CA19645
C ₆ H ₄ NO ₂ CH ₂	—	HCl	—	50JCS2775
2-C ₁₀ H ₇ CH ₂	—	HCl	—	50JCS2775
3-Thienyl	—	HCl	—	72CA19645
Thymyloxymethyl	—	HCl	—	53JCS1636
CO ₂ Et	—	HBr	—	86T2625

R = H) while with alkaline potassium permanganate a bright green color was obtained (41MI1).

Shaw and co-workers during studies into the *de novo* biosynthesis of purine nucleotides demonstrated that 4(5)-aminoimidazole (**25**; R = H) on treatment with a saturated aqueous solution of potassium bicarbonate at 70°C for 15 min gave 4-aminoimidazole-5-carboxylic acid (**38**) in an estimated yield of 40% [71JCS(C)1501]. This and related reactions are discussed in more detail in Section V,B,4.

C. LITERATURE SURVEY

Table II summarizes 4(5)-aminoimidazoles derivatives (**25**), which have been described as either the free base or a simple salt, or were generated *in situ* and used immediately without isolation.

IV. 5-Unsubstituted, 4-Aminoimidazoles

A. SYNTHESIS

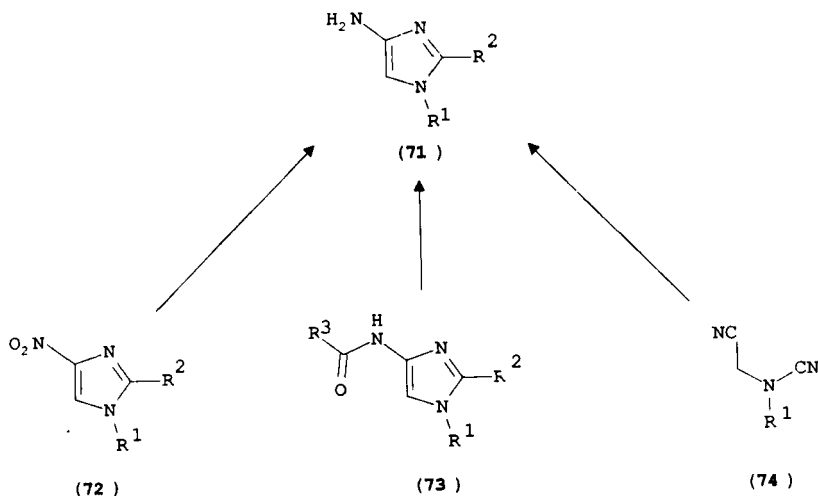
Three approaches to the synthesis of 4-amino-5-unsubstituted imidazoles (**71**) have been described and are summarized in Scheme 7. These are (a) reduction of 4-nitroimidazoles (**72**); (b) hydrolysis of carbamates and amides (**73**); (c) cyclization of nitrile derivatives (**74**).

1. Reduction of 4-Nitroimidazoles

The use of hydrazine hydrate in anhydrous methanol with 5% palladium on charcoal under an inert atmosphere gave excellent results for the reduction of 1-benzyl-4-nitroimidazole (**72**; R¹ = CH₂Ph, R² = H) with compound (**71**; R¹ = CH₂Ph, R² = H) being isolated as its hydrochloride salt (96%) (74JMC1168).

Catalytic hydrogenation of methanolic solutions of the 4-nitroimidazoles (**72**; R¹ = D-glucopyranosyl, D-arabinopyranosyl, D-xylopyranosyl; R² = H) using platinum oxide as catalyst gave the corresponding 4-aminoimidazole nucleosides (**71**; R¹ = D-glucopyranosyl, D-arabinopyranosyl, D-xylopyranosyl; R² = H) (yields; 16, 33, and 25%, respectively), which were apparently isolated as the free bases but no mention of the stability of these compounds was made (72LA67).

A more commonly used catalyst for hydrogenation has been 5% Pd/C in either ethanol or dioxane as solvent. Reduction of the carboxylate

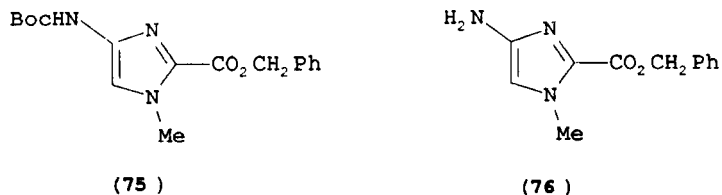


SCHEME 7

derivative (72; R¹ = Me, R² = CO₂Et) gave the product (71; R¹ = Me, R² = CO₂Et) (99%) as a pale yellow powder. This amine darkened slowly on exposure to air [90ACS(B)67]. The same amine (71; R¹ = Me, R² = CO₂Et) was also generated in a mixture of ethyl acetate and methanol using 10% Pd/C as catalyst [92JA5911]. Several 4-aminoimidazoles (71; R¹ = Me, CH₂OAc, CH₂Ph, SO₂NMe₂, *p*-4NH₂C₆H₄, R² = H, Me, *i*Pr), were generated *in situ* in high yield by reduction of the corresponding 4-nitroimidazoles (72). Attempts to isolate these 4-aminoimidazoles were unsuccessful and their solutions were used immediately for further synthesis [92JCS(P1)2779, 92JCS(P1)2789] (see Section IV,B).

2. Hydrolysis of Carbamates and Amides

Treatment of the Boc-protected 4-aminoimidazole (75) (prepared via compound (71; R¹ = Me, R² = CO₂Et) by condensation with *t*-butoxycarbonyl fluoride in the presence of triethylamine) with trifluoro-

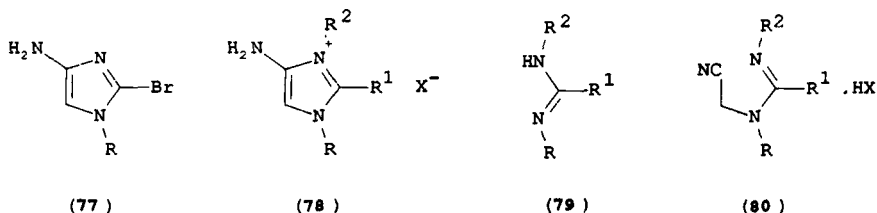


acetic acid gave the 4-aminoimidazole (**76**) (crude yield 85%) as a yellow unstable solid [90ACS(B)67].

3. Cyclization of Nitrile Derivatives

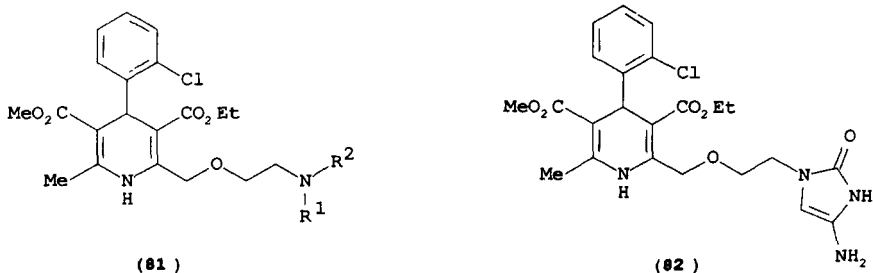
4-Amino-2-bromoimidazoles (**77**) have been prepared by the action of hydrogen bromide on α -cyanoalkylcyanamides (**74**) and were found to display preemergent herbicide activity (64JOC153). These 4-aminoimidazoles (**77**) are unstable in the presence of water and undergo rapid decomposition on treatment with base.

4-Aminoimidazolium salts (**78**) have been synthesized by the reaction of *N,N'*-disubstituted amidines (**79**) with a haloacetonitrile. The formation of the salts (**78**) proceeds via the intermediates (**80**) (71BCJ826, 71JOC3368). These salts (**78**) can be acetylated with acetic anhydride, and the halide ion (X^-) replaced by perchlorate or picrate anions (71BCJ826).



In compounds (78)-(80): X = Cl, Br, I; R, R¹, R² = aryl, alkyl

Treatment of a methanolic solution of the nitrile derivatives (**81**; R¹ = CH₂CN, R² = CONH₂) [prepared in two steps from the calcium antagonist compound (**81**; R¹ = R² = H)] with sodium hydride resulted in facile cyclization, giving the 4-aminoimidazol-2-one derivative (**82**) (53%) (90JMC1805).



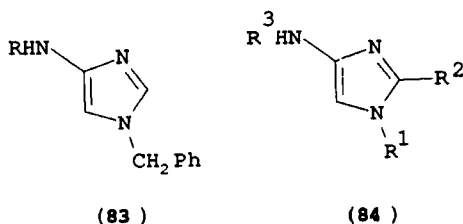
B. CHEMICAL PROPERTIES

1. Acylation

The hydrochloride salt of 4-amino-1-benzylimidazole (**83**; $R = H$) was acetylated readily by acetic anhydride to give the acetamide derivative (**83**; $R = COCH_3$) (55%) (74JMC1168). Treatment with acetic-formic anhydride gave the corresponding formamide (**83**; $R = CHO$).

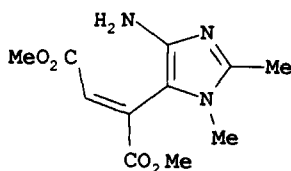
Cyclization of α -cyanoalkyl cyanamides (**74**) with hydrogen bromide gave 4-aminoimidazoles (**77**) as their hydrobromide salts. These compounds (**77**) were found to be unstable as the free base but gave stable *N*-acetyl derivatives (**84**; $R^2 = Br$, $R^3 = COCH_3$) (33–82%) when treated with acetic anhydride in pyridine (64JOC153; 66CA12211).

Formylation of the 4-aminoimidazole (**71**; $R^1 = Me$, $R^2 = CO_2Et$) was achieved by the use of either dicyclohexylcarbodiimide in formic acid or pentafluorophenyl formate in chloroform to give the formamide (**84**; $R^1 = Me$, $R^2 = CO_2Et$, $R^3 = CHO$) in high yield. Similar formylation of compound (**76**) gave the formamide (**84**; $R^1 = Me$, $R^2 = CO_2CH_2Ph$, $R^3 = CHO$) [90ACS(B)67]. Treatment of the 4-aminoimidazole (**71**; $R^1 = Me$, $R^2 = CO_2Et$) with *t*-butyric anhydride in various solvents has been shown to give the *t*-butoxy carbonylated derivative (**84**; $R^1 = Me$, $R^2 = CO_2Et$, $R^3 = Boc$), and almost quantitative yields were achieved by the use of *t*-butyryl fluoride in a mixture of ether and acetonitrile containing triethylamine. Catalytic hydrogenation of 1-methyl-4-nitroimidazole (**72**; $R^1 = Me$, $R^2 = H$) gave the unstable amine (**71**; $R^1 = Me$, $R^2 = H$), which was treated *in situ* with *t*-butyryl fluoride in the presence of potassium carbonate to give the carbamate (**84**; $R^1 = R^2 = Me$, $R^3 = Boc$) [90ACS(B)67]. Similarly, the amine (**71**; $R^1 = Me$, $R^2 = CO_2Et$), which was generated *in situ* from the nitro precursor (**72**; $R^1 = Me$, $R^2 = CO_2Et$), was treated with 1-methyl-4-nitropyrrole-2-carbonyl chloride in dichloromethane solution in the presence of triethylamine to give the amide (**84**; $R^1 = Me$, $R^2 = CO_2Et$, $R^3 = 1\text{-methyl-4-nitropyrrol-2-yl}$) (87%) (92JA5911).

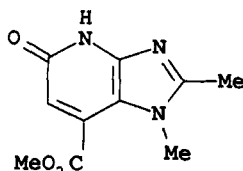


2. Addition Reactions

The reaction of 4-amino-1,2-dimethyl imidazole (**71**; $R^1 = R^2 = \text{Me}$) in dioxane solution with dimethylacetylene dicarboxylate (DMAD) gave the C-addition product (**85**) (50%) [92JCS(P1)2779]. This adduct (**85**) underwent thermal cyclization to give the imidazo[4,5-*b*]pyridine (**86**). It is interesting to note the preferred C-addition with this reagent (DMAD) compared to the observed *N*-addition of 4-aminoimidazoles with the reagents (**58**)–(**62**) (Section IV,B,3). Preference for addition on the ring carbon atom can probably be attributed to the softness of the reagent (see Section VI,C).



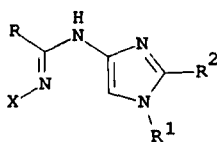
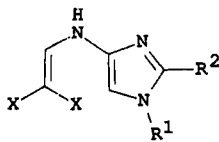
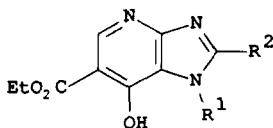
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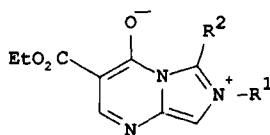
(86)

3. Addition–Elimination Reactions

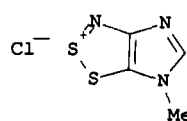
4-Aminoimidazoles (**71**) condense with the reagents (**58**; $R = \text{H}, \text{Me}$), (**60**; $R = \text{H}$), (**61**) and (**62**) to give exclusively *N*-adducts of the general types (**87**) and (**88**) [92JCS(P1)2789]. These adducts are formed in good yield, but their synthetic potential has not been fully explored. Cyclization

(87) $X = \text{CN}, \text{CO}_2\text{Et}$ (88) $X = \text{CN}, \text{CO}_2\text{Et}$ 

(89)



(90)



(91)

of the adduct (**88**; $X = \text{CO}_2\text{Et}$, $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) using a mixture of acetic anhydride and sulfuric acid gave a mixture of the imidazo[4,5-*b*]pyridine (**89**; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) (11%) and the imidazo[1,5-*a*]pyrimidine (**90**; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) (29%). The cycloaddition reactions of this mesomeric betaine (**90**; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$) have been described [92JCS(P1)2789].

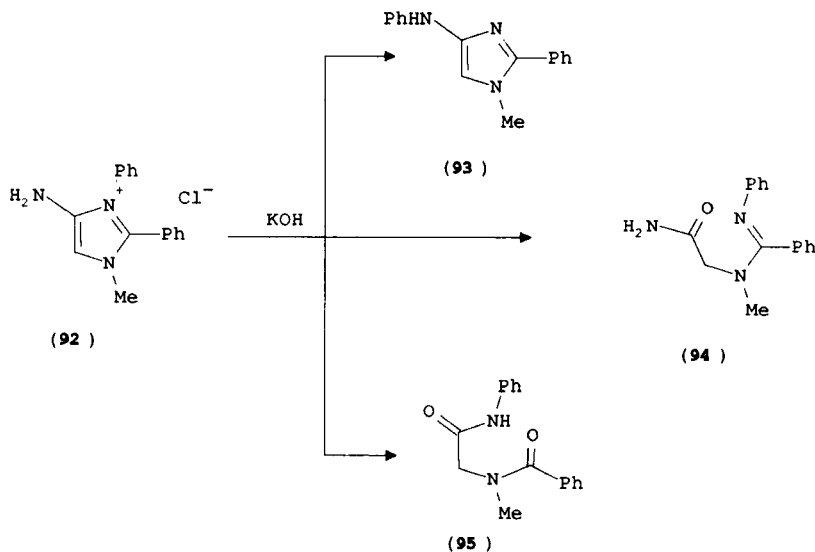
Reaction of 1-methyl-4-aminoimidazole (**71**; $R^1 = \text{Me}$, $R^2 = \text{H}$) with sulfur monochloride (S_2Cl_2) gave a product that was isolated and assumed to be the imidazo[4,5-*d*]-1,2,3-dithiazole (**91**) (56%) by analogy with other hetero-Herz reactions (84JOC1224).

4. Miscellaneous Reactions

The quaternized salt (**92**) has been shown to react in different ways with aqueous potassium hydroxide solution, depending on reaction time, temperature, and base concentration, to give the strikingly different products (**93**), (**94**), and (**95**) (Scheme 8) (71JOC3368).

C. LITERATURE SURVEY

Table III summarizes 4-aminoimidazole derivatives (**71**), which have been described either as the free base or as a simple salt, or have been generated *in situ* and used immediately without isolation.



SCHEME 8

TABLE III
KNOWN 4-AMINOIMIDAZOLE DERIVATIVES (71)

(71)

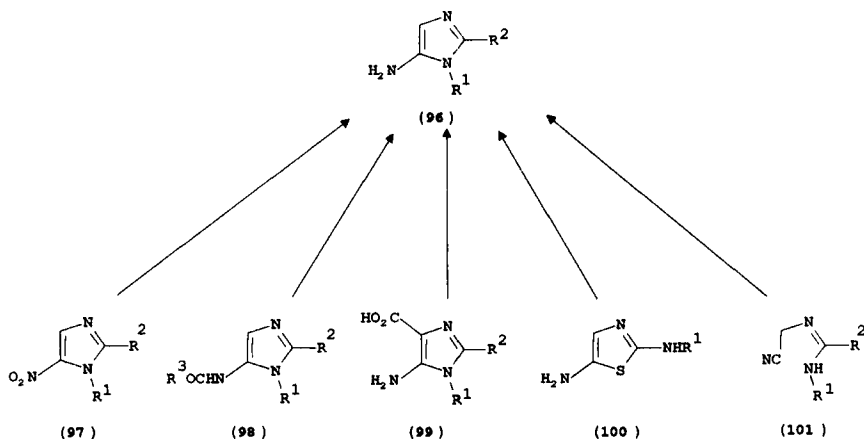
R ¹	R ²	Free base	Salt	<i>In situ</i>	Reference
Me	H	—	HCl	—	84JOC1224
CH ₂ Ph	H	—	HCl	—	74JMC1168
CH ₂ Ph	H	—	—	✓	92JCS(P1)2779
D-Glucopyranosyl	H	✓	—	—	72LA67
D-Arabinopyranosyl	H	✓	—	—	72LA67
D-Xylopyranosyl	H	✓	—	—	72LA67
Me	CO ₂ Et	✓	—	—	90ACS(B)67
Me	CO ₂ CH ₂ Ph	✓	—	—	90ACS(B)67
CH ₂ OAc	H	—	—	✓	92JCS(P1)2779
CH ₂ OAc	Me	—	—	✓	92JCS(P1)2779
Me	Me	—	—	✓	92JCS(P1)2779
Me	<i>i</i> Pr	—	—	✓	92JCS(P1)2779
Me	CO ₂ Et	—	—	✓	92JA5911
CH ₂ Ph	Me	—	—	✓	92JCS(P1)2779
SO ₂ NMe ₂	H	—	—	✓	92JCS(P1)2779
<i>p</i> -NH ₂ C ₆ H ₄	Me	—	—	✓	92JCS(P1)2779
Amlodipinyl	OH ^a	—	Hydrate	—	90JMC1805
Me	Br	—	HBr	—	64JOC153
Et	Br	—	HBr	—	64JOC153
Bu	Br	—	HBr	—	64JOC153
Ph	Br	—	HBr	—	64JOC153
CH ₂ Ph	Br	—	HBr	—	64JOC153

^a This example exists as the oxo tautomer.

V. 4-Unsubstituted, 5-Aminoimidazoles

A. SYNTHESIS

Five approaches to the synthesis of 5-amino-4-unsubstituted imidazoles (**96**) have been described and are summarized in Scheme 9. These are (a) reduction of 5-nitroimidazoles (**97**), (b) hydrolysis of carbamates and amides (**98**), (c) decarboxylation of imidazole carboxylic acids (**99**), (d) ring transformations of 5-aminothiazoles (**100**), and (e) cyclisation of nitrile derivatives (**101**).



SCHEME 9

1. Reduction of 5-Nitroimidazoles

Successful methods for the reduction of 5-nitroimidazoles (**97**) have largely involved catalytic hydrogenation. 5-Nitroimidazoles (**97**) have been reduced in ethyl acetate solution in the presence of sodium sulfate using Raney nickel [82IJC(B)1087]. Using this method, the 2-benzoyl derivative (**96**; $R^1 = \text{Me}$, $R^2 = \text{COPh}$) was isolated as the free base in a pure state (46%). 5-Amino-2-methanesulfonyl-1-methylimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$) was also synthesized by this method from the corresponding 5-nitroimidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$) but could not be purified. However, the pure 5-aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$) was obtained (34%) by hydrogenation of compound (**97**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$) in ethyl acetate solution using 10% palladium on charcoal as catalyst and recrystallization of the crude product from a mixture of methanol and ether.

The isolation of these compounds (**97**; $R^1 = \text{Me}$, $R^2 = \text{COPh}$, SO_2Me) was no doubt aided by the presence of electron-withdrawing groups at the 2-position, which stabilize the electron-rich aminoimidazole ring. Even so, the authors noted [82IJC(B)1087] that these amines decomposed on keeping.

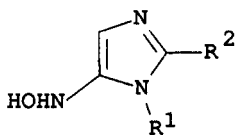
Early studies on the metabolism of the antibacterial drug metronidazole (**97**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) failed to isolate or even detect an aminoimidazole metabolite (66MI1; 68MI1; 75MI1; 79MI1; 83MI1), but later studies demonstrated that indeed the aminoimidazole (**96**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) was a major metabolite (87MI1). Reduction of this compound (**97**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) was achieved synthetically in absolute ethanol using 5% palladium on charcoal as catalyst and the corresponding 5-aminoimidazole (**96**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) was obtained as an

impure solid (82MI1; 87MI1). Later studies demonstrated that the choice of solvent was important and this aminoimidazole (**96**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) was obtained in a pure crystalline state by catalytic hydrogenation (Pd/C) of the nitroimidazole (**97**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) in 1,4-dioxane solution [89CC551; 92JCS(P1)2779]. Using this procedure, the 5-aminoimidazoles (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$, Me) were also obtained as crystalline solids [92JCS(P1)2779]. Several other nitroimidazoles were reduced to give solutions of corresponding 5-aminoimidazoles (**96**), which were used *in situ* for further synthesis [92JCS(P1)2779].

1-Methyl-5-nitro-2-(2'-pyrimidyl) imidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$), which has antitrichomonal properties, was the subject of metabolic studies in both man and rat (74JPS293). A metabolite was characterized by IR, NMR, and mass spectroscopy and identified as 5-acetamido-1-methyl-2-(2'-pyrimidyl)imidazole, suggesting that 5-amino-1-methyl-2-(2'-pyrimidyl)imidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) was an intermediate in the metabolic pathway. This aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) was produced synthetically by treatment of an acetic acid solution of the corresponding nitroimidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) with zinc powder. However, the product (**96**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) was found to be unstable and was characterized as the acetamide derivative by subsequent treatment with acetic anhydride (74JPS293).

The relative instability of the 5-aminoimidazoles has led to failure to detect aminoimidazole metabolites during other metabolic studies of corresponding nitroimidazole antibacterial agents [63N(L)1024; 73MI1, 73MI2; 79MI2].

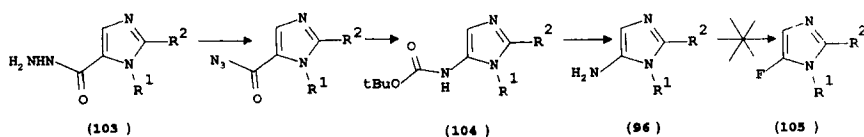
Polarographic reduction of 1-methyl-5-nitroimidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{H}$) has been shown to proceed in two distinct steps, probably via the hydroxylamine derivative (**102**), to give the amino compound (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) (62CR2603).



(102)

2. Hydrolysis of Carbamates

This method of preparation of 5-aminoimidazoles remains unexplored with only one example reported. Cohen and Kirk applied their successful method of preparing 4-fluoroimidazole (via 4-aminoimidazole (**25**; $R = \text{H}$)) (73JA4619, 73JOC3647) (Section III,A,2) to 5-aminoimidazoles (**96**)



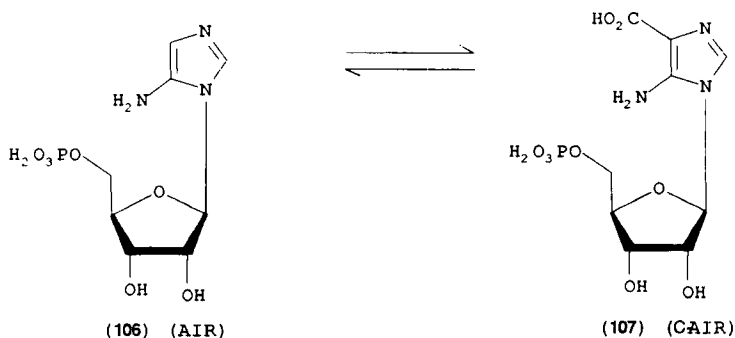
SCHEME 10

(78JOC3570). Diazotization of 1-methylimidazole-5-carbohydrazide (**103**) followed by treatment with *t*-butanol gave the carbamate (**104**), which was dissolved in cold tetrafluoroboric acid: when evolution of gas had ceased, the solution was treated with sodium nitrite and irradiated. However, unlike the 4-aminoimidazoles (Section III,A,2), this reaction produced none of the desired 5-fluoro-1-methylimidazole (**105**) (Scheme 10). Although 5-amino-1-methylimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) was almost certainly formed, ultraviolet spectral analysis showed only traces of a diazonium chromophore after addition of nitrite, indicating compound (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) to be extremely unstable under the acidic reaction conditions (78JOC3570).

3. Decarboxylation of Imidazole Carboxylic Acids

During their studies on the biosynthesis of purines (57JA1511; 59JBC1791, 59JBC1799), Lukens and co-workers recognized that AIR (**106**) was biologically and chemically interconvertible with 5-aminoimidazole-4-carboxylic acid ribonucleotide (C-AIR) (**107**) (Scheme 11).

Attempts to isolate pure C-AIR (**107**) were unsuccessful due to its instability in acid solution and toward heat resulting in decarboxylation giving AIR (**106**) (57JA1511). Using UV spectrometry, transformation of C-AIR (**107**) to AIR (**106**) was shown to occur in 2–3 h at room temperature in 0.25 *N* sulfuric acid solution (59JBC1799). The decarboxylation of C-AIR

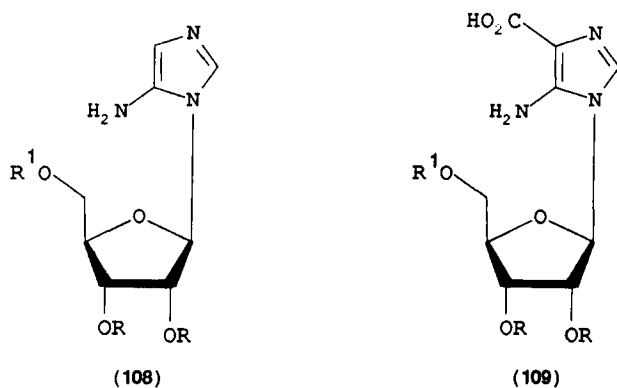


SCHEME 11

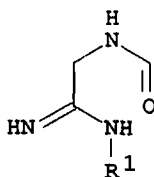
(107) was also the subject of studies by Shaw and co-workers [62JCS(C)2937; 65CC563], who investigated the mechanism noting that (a) the rate of decarboxylation increased with increase in basic character of the constituents of the buffered solutions at constant pH; (b) the rate of decarboxylation was greatly reduced by the presence of bivalent (especially transition) metal ions at a pH greater than 4.5; and (c) with the enzymatic decarboxylation, nickel ions completely inhibited the transformation at pH 8.2 at a concentration of 10^{-4} M.

Estimates of the purity of the natural aminoribotide AIR (106) obtained by decarboxylation of C-AIR (107) have been put in the order of 30–60% [57JBC1005; 66JCS(C)2270].

Recent work into studies of analogues of AIR (106) utilized the facile decarboxylation of C-AIR (107) for the synthetic methodology (88PNA7174; 90JA4891). Thus, the acetyl nucleoside (108; $R=R^1=Ac$) was obtained from the acid precursor (109; $R=R^1=Ac$) by treatment at $35^\circ C$ in a buffered solution at pH 4.8. The product (108; $R=R^1=Ac$) was extracted and purified chromatographically giving the pure solid aminoimidazole (108; $R=R^1=Ac$) (65%). The aminoimidazole ribonucleoside (108; $R=R^1=H$) (88%) was similarly obtained from the corresponding acid (109; $R=R^1=H$) (88PNA7174). An extension of these studies (90JA4891) resulted in the synthesis of AIR (106) and the synthesis of all three possible ^{15}N -labeled analogues of the acetyl nucleoside (108; $R=R^1=Ac$).



The relative inaccessibility of C-AIR (107) promoted Shaw and co-workers [66JCS(C)2270] to use the 5-aminoimidazole-4-carboxylate (111; $R=H$) as a model compound since this was readily obtained as a crystalline sodium salt, in two steps from ethyl *N*-(cyano-ethoxycarbonylmethyl)formimidate (110) and cyclohexylamine (Scheme 12) [62JCS(C)2937]. 5-Amino-1-cyclohexylimidazole (112; $R=H$) was obtained as the picrate salt (22%) from the sodium salt of the acid (111; $R=H$) by treatment of

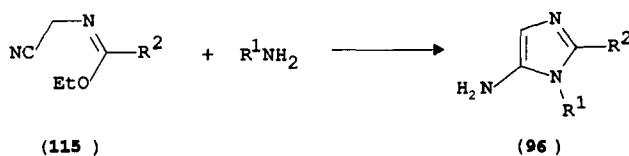


(114)

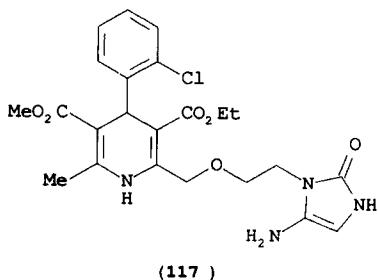
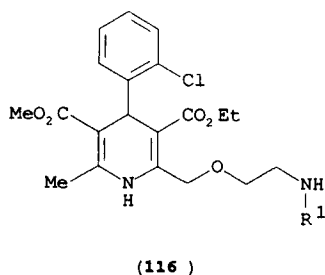
available cyclohexyl analogue (**114**; $R^1 = \text{cyclohexyl}$) (67CC799). The formylglycinimidine (**114**; $R^1 = \text{cyclohexyl}$) was cyclized to the 5-aminoimidazole (**96**; $R^1 = \text{cyclohexyl}$, $R^2 = \text{H}$) by heating at 150°C for 30 min or by heating in phosphoryl chloride at 90°C for 30 min in estimated yields of 5–15%.

A more versatile synthesis of 5-aminoimidazoles (**96**) involved treatment of the imidate (**115**) with appropriate primary amines (59JCS1648; 61JCS4845) (Scheme 13). For example, treatment of ethyl *N*-(cyanomethyl)-formimidate (**115**; $R^2 = \text{H}$) with either methylamine or ethylamine gave the corresponding 5-aminoimidazoles (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) (40%) and (**96**; $R^1 = \text{Et}$, $R^2 = \text{H}$) (30%) (59JCS1648). Similarly, treatment with hydrazine gave the diamino derivatives (**96**; $R^1 = \text{Et}$, $R^2 = \text{H}$) (47%) (61JCS4845), which were characterized as picrate salts. The authors also reported the synthesis of the ribonucleoside (**96**; $R^1 = \text{ribosyl}$, $R^2 = \text{H}$), although its isolation was not achieved (59JCS1648).

Extension of this procedure (Scheme 13) to substituted imidates provided a synthesis of 2-substituted 5-aminoimidazoles [59JCS1648; 74BSF(2)1453; 78JHC937]. Thus, treatment of ethyl *N*-(cyanomethyl)acetimidate (**115**; $R^2 = \text{Me}$) with either methylamine or *D*-galactosylamine gave the 5-aminoimidazoles (**96**; $R^1 = R^2 = \text{Me}$) and (**96**; $R^1 = \text{galactostyl}$, $R^2 = \text{Me}$), respectively, which were characterized as picrate salts (59JCS1648). Also, treatment of ethyl *N*-(cyanomethyl)benzimidate (**115**; $R^2 = \text{Ph}$) with either hydrazine or phenyl hydrazine gave the 1,5-diamino-2-phenylimidazole derivatives (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) (92%) and (**96**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) (44%), respectively [74BSF(2)1453; 78JHC937]. The 2-benzyl-substituted analogues (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{CH}_2\text{Ph}$) and (**96**; $R^1 = \text{NHPh}$, $R^2 = \text{CH}_2\text{Ph}$) were also obtained by use of the imidate (**115**;



SCHEME 13



$R^2 = \text{CH}_2\text{Ph}$ [74BSF(2)1453]. The unexpected stability of the latter four examples was attributed by the authors to the presence of phenyl substituents (83JHC1015).

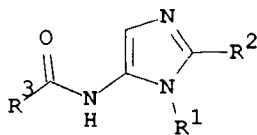
Treatment of a methanolic solution of the nitrile derivative (**116**; $R^1 = \text{CONHCH}_2\text{CN}$) [prepared in two steps from the calcium antagonist compound (**116**; $R^1 = \text{H}$)] with sodium hydride resulted in facile cyclization giving the 5-aminoimidazol-2-one derivative (**117**), which was isolated as the hydrochloride salt (29%) (90JMC1805).

B. CHEMICAL PROPERTIES

1. Acylation

The instability of 5-aminoimidazoles (**96**) has led to *in situ* acylation being used to obtain stable compounds and using this approach several derivatives have been prepared. For example, a solution of the appropriate 5-nitroimidazole (**97**) in ethyl acetate was reduced with Raney nickel, and the resulting solution of 5-aminoimidazole (**96**) then treated with an acid chloride to give the amides (**118**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$, COPh , $R^3 = \text{alkyl}$, aryl , hetaryl) (25–45%) [82IJC(B)1087].

A slightly modified procedure facilitated the synthesis of the acetamide (**118**; $R^1 = \text{Me}$, $R^2 = 3\text{-methanesulfonyl-imidazolidin-2-on-1-yl}$, $R^3 = \text{Me}$). Thus, a solution of the requisite 5-nitroimidazole (**97**; $R^1 = \text{Me}$, $R^2 = 3\text{-methanesulfonyl-imidazolidin-2-on-1-yl}$) in a mixture of dimethylform-



amide and ethyl acetate was reduced with Raney nickel and the aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = 3\text{-methanesulfonyl-imidazolidin-2-on-1-yl}$) formed was treated with acetic anhydride *in situ* to give the amide (**118**; $R^1 = \text{Me}$, $R^2 = 3\text{-methanesulfonyl-imidazolidin-2-on-1-yl}$, $R^3 = \text{Me}$) (20%) [82IJC(B)1087].

The antitrichomonal compound 1-methyl-5-nitro-2-(2'-pyrimidyl)imidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) has been shown to be metabolized to the corresponding acetamide (**118**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$, $R^3 = \text{Me}$) in both rats and humans (74JPS293). The acetamide (**118**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$, $R^3 = \text{Me}$) was also produced synthetically by reduction of a solution of the nitroimidazole (**97**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) in acetic acid with zinc powder and subsequent treatment of the aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$) *in situ* with acetic anhydride to give the acetamide (**118**; $R^1 = \text{Me}$, $R^2 = \text{pyrimid-2-yl}$, $R^3 = \text{Me}$) (4%) (74JPS293).

The acetamido derivative (**118**; $R^1 = \text{triacylribonucleoside}$, $R^2 = \text{H}$, $R^3 = \text{Me}$) (86%) was prepared from a mixture of isomeric precursors (**96**; $R^1 = \text{diacylribonucleoside}$, $R^2 = \text{H}$) by treatment of a dichloromethane solution with acetic anhydride in the presence of pyridine (90JA4891).

During their studies with 1,5-diaminoimidazoles (**96**; $R^1 = \text{NHR}$, $R^2 = \text{Ph}$), French workers isolated the amide (**118**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$, $R^3 = \text{COCH}_2\text{COMe}$) (5%) after heating a solution of compound (**96**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) in xylene with ethyl acetoacetate. The major product of the reaction was an imidazo[4,5-*b*]pyridone (Section V,B,8,a) (78JHC937).

2. Diazotization

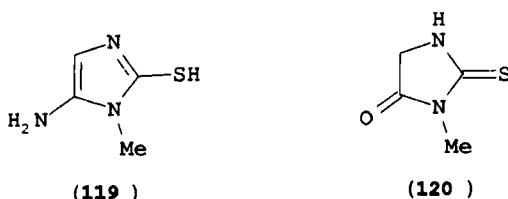
Although 5-amino-4-unsubstituted imidazoles (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$, SH) have limited stability, their hydrochloride salts can be diazotized, and the diazonium salt coupled with β -naphthol to give red dyes (48JCS2028). A variation of this reaction was used as a means of monitoring the progress of reactions during studies into the *de novo* biosynthesis of purine nucleotides [66JCS(C)2270]: diazotization of the aminoimidazole and subsequent coupling with naphthylethylenediamine gave a characteristic dye with maximum absorbance in the UV spectrum in the order of 500 nm. For example, the dyes resulting from the 5-aminoimidazoles (**96**; $R^1 = \text{cyclohexyl}$, $R^2 = \text{H}$; $R^1 = \text{pyrid-2-yl}$, $R^2 = \text{H}$, $R^1 = R^2 = \text{Me}$) gave maximum absorbances of λ_{max} 500 nm [66JCS(C)2270], λ_{max} 505 nm [80JCS(P1)2316], and λ_{max} 495 nm (63MI1).

An attempted preparation of 5-fluoro-1-methylimidazole via diazotization of the aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) was unsuccessful, probably due to the instability of the 5-aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) in

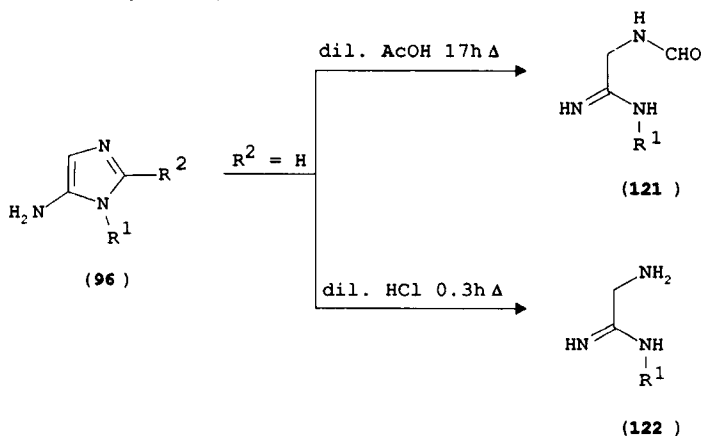
the aqueous acidic solution (78JOC3570) (see Section V,A,2). In contrast to the unsuccessful diazotization of 5-amino-1-methylimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{H}$) in tetrafluoroboric acid solution, the corresponding hydrochloride salt was diazotized in nitrous acid solution as demonstrated by the formation of a red dye produced by subsequent coupling of the diazotized material with β -naphthol (48JCS2028).

3. Hydrolysis

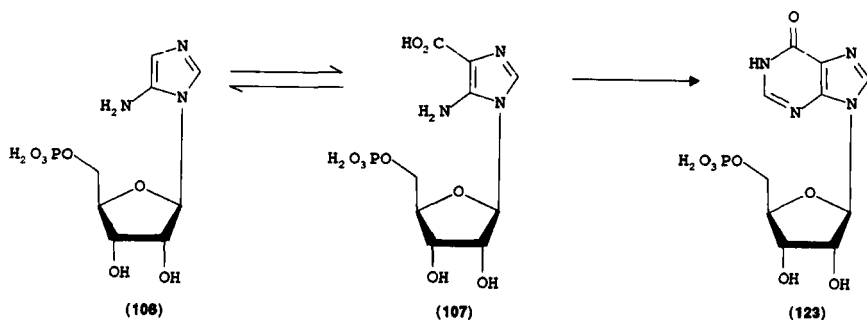
3-Methyl-2-thiohydantoin (**120**) (40%) was found to be the hydrolysis product when a concentrated hydrochloric acid solution of 5-amino-2-mercapto-1-methylimidazole (**119**) was heated under reflux (48JCS2028).



The 5-aminoimidazoles (**96**; $R^1 = \text{cyclohexyl}$, $R^2 = \text{H}$) and (**96**; $R^1 = \text{ribonucleotide}$, $R^2 = \text{H}$) have been shown to suffer ring cleavage by the action of hot dilute acetic acid, giving the formylglycineamidines (**121**; $R^1 = \text{cyclohexyl}$) and (**121**; $R^1 = \text{ribonucleotide}$) [66JCS(C)2270]. Further hydrolysis is observed by treatment of the compounds (**96**; $R^1 = \text{cyclohexyl}$, $R^2 = \text{H}$) and (**96**; $R^1 = \text{ribonucleotide}$, $R^2 = \text{H}$) with hot dilute hydrochloric acid, giving the aminoamidines (**122**; $R^1 = \text{cyclohexyl}$) and (**122**; $R^1 = \text{ribonucleotide}$) (Scheme 14) [66JCS(C)2270].



SCHEME 14



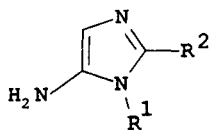
SCHEME 15

4. Carboxylation

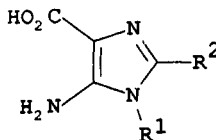
The synthesis of inosinic acid (**123**) from AIR (**106**) using soluble avian liver enzymes has been shown to proceed in several steps. The first step involves the formation of C-AIR (**107**) by carboxylation of the aminoimidazole (**106**) (Scheme 15) (57JA1511).

This process (**106** \rightarrow **107**) required the incubation of an aqueous mixture of AIR (**106**), potassium carbonate, and enzyme (AIR carboxylase). The equilibrium of the carboxylation reaction was shown to lie to the left (59JBC1799), but in the presence of 0.3 *M* aqueous potassium bicarbonate solution, yields of C-AIR (**107**) approaching 50% were obtained.

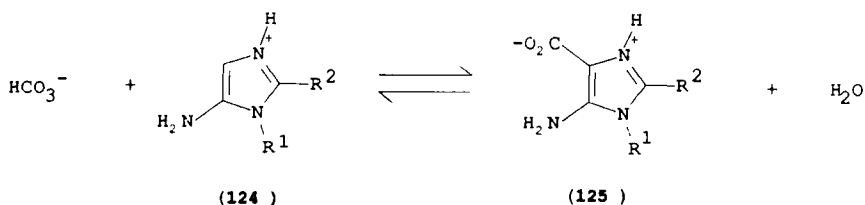
It was subsequently demonstrated that the formation of C-AIR (**107**) from AIR (**106**) required only bicarbonate and that an enzyme was unnecessary [67CC799; 71JCS(C)1501]. A more detailed study of the carboxylation was undertaken using the model compound 5-amino-1-cyclohexylimidazole (**96**; R^1 =cyclohexyl, R^2 =H) [67CC799; 71JCS(C)-1501]. It was found that the best yield (40%) of carboxylated compound (**99**; R^1 =cyclohexyl, R^2 =H) was obtained by treatment of the aminoimidazole (**96**; R^1 =cyclohexyl, R^2 =H) with an saturated aqueous solution of potassium bicarbonate at 70°C for 15 min. Similar results were obtained for the carboxylation of 5-amino-1-cyclohexyl-2-methylimidazole (**96**; R^1 =cyclohexyl, R^2 =Me) to the corresponding carboxylic acid (**99**;



(96)



(99)



SCHEME 16

$\text{R}^1 = \text{cyclohexyl}$, $\text{R}^2 = \text{Me}$) [67CC799; 71JCS(C)1501] and carboxylation of 5-amino-1-methylimidazole (**96**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) to the corresponding carboxylic acid (**99**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) (87ZOB692).

It was considered that an aqueous solution of bicarbonate contained carbonic acid, carbonate, and carbon dioxide in addition to bicarbonate [67CC799; 71JCS(C)1501]. Experiments were conducted to determine the carboxylating species and it was shown that carboxylation could not be achieved with carbon dioxide nor with carbonate. It was thus concluded that the likely carboxylating species was bicarbonate anion and that the process could be visualized as involving addition of the protonated species (124) to the bicarbonate anion, giving the observed product (125) (Scheme 16).

5. Addition Reactions

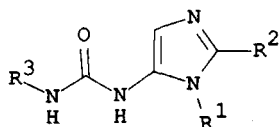
a. *With Isocyanates and Isothiocyanates.* Addition of isocyanates or isothiocyanates to 5-aminoimidazoles (**96**) is a simple method of obtaining stable derivatives and this method has proved useful in demonstrating the formation of 5-aminoimidazoles (**96**). Addition of methylisocyanate to a solution of 5-amino-2-mercapto-1-methylimidazole (**96**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{SH}$) in pyridine gave *N*-(2-mercapto-1-methylimidazol-5-yl)-*N'*-methyl urea (**126**; $\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{SH}$) (40%) (48JCS2028). Similarly, reaction of ethyl acetate solutions of 5-aminoimidazoles (**96**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{COPh}$, SO_2CH_3 , SOCH_3) with isothiocyanates gave the corresponding thioureas (**127**) [82IJC(B)1087] (Table IV). Dioxane solutions of 5-aminoimidazoles (**96**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}$, *i*Pr) and (**96**; $\text{R}^1 = \text{CH}_2\text{CH}_2\text{OH}$, $\text{R}^2 = \text{Me}$) on treatment with isocyanates or isothiocyanates gave the respective ureas (**126**) and thioureas (**127**) in good overall yield [92JCS(P1)2779] (Table IV).

b. *With Diketene.* Addition of diketene to a dioxane solution of 5-amino-1,2-dimethylimidazole (**96**; $\text{R}^1 = \text{R}^2 = \text{Me}$) (generated *in situ* by catalytic hydrogenation of the nitroimidazole precursor—see Section V,A,1) gave the expected amide (**128**) (47%) [92JCS(P1)2779].

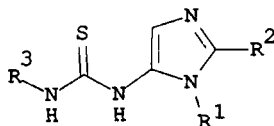
TABLE IV
UREAS (126) AND THIUREAS (127) OBTAINED FROM 5-AMINOIMIDAZOLES (96)

(126)	R ¹	R ²	R ³	Yield (%)	Reference
(126)	Me	SH	Me	40	48JCS2028
(126)	Me	Me	3,4-Cl ₂ C ₆ H ₃	47	92JCS(P1)2779
(126)	Me	Me	3-Cl-4-MeC ₆ H ₃	38	92JCS(P1)2779
(126)	Me	<i>i</i> Pr	3,4-Cl ₂ C ₆ H ₃	51	92JCS(P1)2779
(126)	Me	<i>i</i> Pr	3-Cl-4-MeC ₆ H ₃	37	92JCS(P1)2779
(126)	Me	<i>i</i> Pr	4-MeC ₆ H ₄ SO ₂	15	92JCS(P1)2779
(126)	CH ₂ CH ₂ OH	Me	3-Cl-4-MeC ₆ H ₃	3	92JCS(P1)2779
(127)	Me	Me	Ph	55	92JCS(P1)2779
(127)	Me	<i>i</i> Pr	Ph	24	92JCS(P1)2779
(127)	Me	COPh	CO ₂ Et	35	82IJC(B)1087
(127)	Me	COPh	4-MeC ₆ H ₄ SO ₂	— ^a	82IJC(B)1087
(127)	Me	COPh	COPh	32	82IJC(B)1087
(127)	Me	SO ₂ Me	CO ₂ Et	45	82IJC(B)1087
(127)	Me	SO ₂ Me	4-MeC ₆ H ₄ SO ₂	60	82IJC(B)1087
(127)	Me	SOMe	CO ₂ Et	25	82IJC(B)1087
(127)	Me	SOMe	COPh	25	82IJC(B)1087

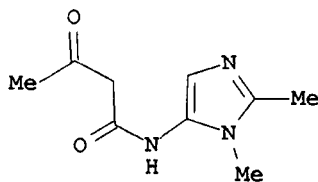
^a Yield not reported.



(126)

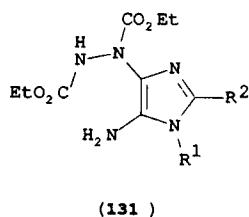
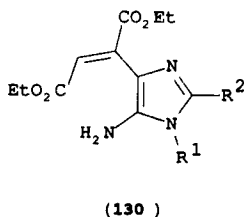
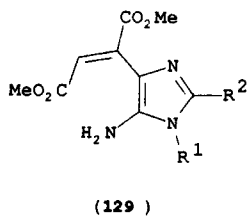


(127)



(128)

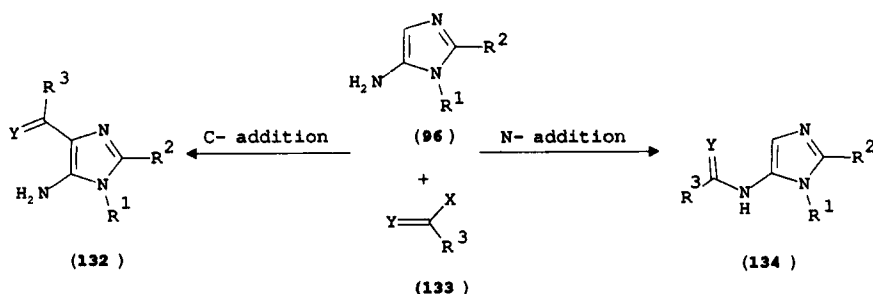
c. *With Dialkylacetylene Dicarboxylates and Dialkylazodicarboxylates.* Acetonitrile solutions of 5-aminoimidazoles (**96**) when treated with dialkylacetylene dicarboxylates afford the crystalline 4-substituted derivatives (**129**; $R^1 = R^2 = \text{Me}$; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$; $R^1 = \text{Me}$, $R^2 = i\text{Pr}$) and (**130**; $R^1 = R^2 = \text{Me}$). This C-addition of the electrophile is synthetically (but not mechanistically) comparable to the carboxylation of AIR (**106**) during purine biosynthesis (see Section V,B,4) and has been rationalized in terms of frontier-orbital interactions based on the results of semiempirical molecular orbital calculations [92JCS(P1)2779] (see Section VI,C). The stereochemistry of the olefinic bond in the products (**129**) and (**130**) was not established, but it was assumed that the products were fumarates. These derivatives (**129**) and (**130**) provided a convenient route to imidazo[4,5-*b*]pyridines (see Section V,B,7,a). Similar products were obtained by the reaction between 5-aminoimidazoles (**96**) and diethyl azodicarboxylate. Thus, treatment of a solution of the 5-aminoimidazole (**96**; $R^1 = R^2 = \text{Me}$) in acetonitrile with diethyl azodicarboxylate gave the crystalline hydrazo derivative (**131**; $R^1 = R^2 = \text{Me}$) [92JCS(P1)2779].



6. Addition-Elimination Reactions

Two modes of addition-elimination reaction between 5-aminoimidazoles (**96**) and reagents of the general type (**133**) (Scheme 17) have been observed [92JCS(P1)2789]. In some cases N-addition takes place, leading to the products (**134**), whereas with other reagents C-addition occurs giving the isomeric products (**132**) (Scheme 17). The preferred mode of reaction (C- or N-addition) appears to be determined by the character of the reagents (**133**), although there is some evidence that the nature of the 2-substituent can also influence the mode of reaction.

With ethoxymethylenemalononitrile (**136**), C-addition appears to be the only mode of reaction with simple 5-aminoimidazole derivatives. Typically, reaction of 5-amino-1,2-dimethylimidazole (**96**; $R^1 = R^2 = \text{Me}$) with the reagent (**136**) in dioxane solution gave an 84% yield of the product (**144**; $R^1 = R^2 = \text{Me}$). In contrast, reaction of the same amine with diethyl ethoxymethylenemalonate (**135**) in dioxane solution gave exclusively an



SCHEME 17

86% yield of the product (**146**; $R^1 = R^2 = \text{Me}$) formed via N-addition. When the same reaction was carried out in ethanol solution, a small yield (5%) of the isomeric C-addition product (**143**; $R^1 = R^2 = \text{Me}$) was also formed [89CC551; 92JCS(P1)2789]. Evidence that ring substituents can also influence the mode of reaction is provided by the observation that the 2-mercapto derivative (**96**; $R^1 = \text{Me}$, $R^2 = \text{SH}$) reacts with diethyl ethoxy-methylenemalonate (**135**) to give exclusively the C-addition product (**143**; $R^1 = \text{Me}$, $R^2 = \text{SH}$) (78H241). Addition-elimination reactions of 1,5-diaminoimidazoles (**96**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$, CH_2Ph , $i\text{Pr}$) with the imidates (**140**) and (**141**) in ethanolic or xylene solutions were reported to give exclusively N-adducts, but yields were not recorded (85MI1).

The modes of reaction of several 5-aminoimidazoles (**96**) with the reagents (**135**–**142**) are summarized in Table V. The variation of product structure with reagent is clearly discernable. The preference for C- or N-addition has been interpreted in terms of a frontier orbital analysis of the reactants [92JCS(P1)2779, 92JCS(P1)2789] (see Section VI,C). The

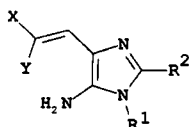
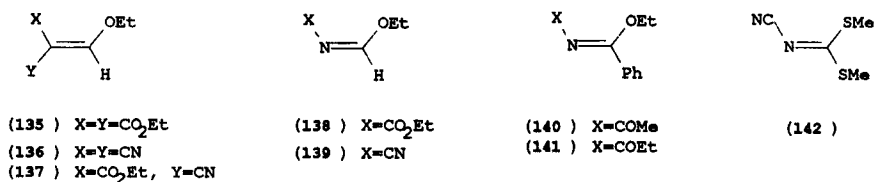
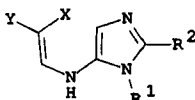
(143) $X=Y=\text{CO}_2\text{Et}$ (144) $X=Y=\text{CN}$ (145) $X=\text{CO}_2\text{Et}$, $Y=\text{CN}$ (146) $X=Y=\text{CO}_2\text{Et}$ (147) $X=Y=\text{CN}$

TABLE V
ADDITION-ELIMINATION REACTION PRODUCTS OF 5-AMINOIMIDAZOLES (96)

The diagram shows the chemical structure of 5-aminoimidazole (96). It is a five-membered ring with two nitrogen atoms. One nitrogen is at the bottom position and is substituted with an R¹ group. The other nitrogen is at the top position. A double bond is located between the two nitrogens. A carbon atom at the 4-position is substituted with an R² group. A carbon atom at the 5-position is substituted with an amino group (H₂N). Two arrows point to the structure: one labeled 'N-addition' pointing to the amino group, and another labeled 'C-addition' pointing to the carbon at the 2-position.

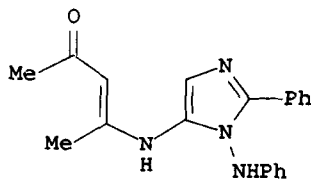
Amine (96)		Reagent (solvent)	Product (%)	
R ¹	R ₂		N-addition	C-addition
Me	Me	135 (ethanol)	65	5
		(dioxane)	86	—
Me	H	135 (ethanol)	62	—
CH ₂ CH ₂ OH	Me	135 (ethanol)	32	—
		(dioxane)	44	—
Me	<i>i</i> Pr	135 (ethanol)	64	5
Me	CH ₂ CH ₂ Ph	135 (ethanol)	43	3
Me	SH	135 (DMF)	—	^a
Me	Me	136 (dioxane)	—	84
CH ₂ CH ₂ OH	Me	136 (dioxane)	—	72
Me	<i>i</i> Pr	136 (dioxane)	—	57
Me	Me	137 (dioxane)	—	46
CH ₂ CH ₂ OH	Me	137 (dioxane)	—	72
Me	<i>i</i> Pr	137 (dioxane)	—	67
Me	Me	138 (dioxane)	49	—
Me	H	138 (dioxane)	52	—
CH ₂ CH ₂ OH	Me	138 (dioxane)	33	—
Me	Me	139 (dioxane)	26	23
Me	H	139 (dioxane)	42	4
CH ₂ CH ₂ OH	Me	139 (dioxane)	—	8
Me	<i>i</i> Pr	139 (dioxane)	11	36
Me	Me	142 (dioxane)	—	47
Me	H	142 (dioxane)	32	10
CH ₂ CH ₂ OH	Me	142 (dioxane)	—	11

^a Exclusive C-addition, but yield not reported.

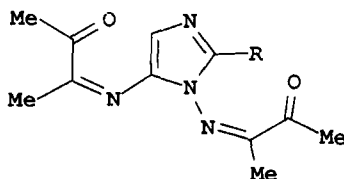
addition-elimination products from these reactions have been shown to be useful intermediates for the synthesis of a number of bicyclic and polycyclic heterocyclic systems, and these are discussed in Section V.B.7.

Condensation reactions of some 1,5-diaminoimidazole derivatives have also been reported. Reaction of 5-amino-1-anilino-2-phenylimidazole (**96**;

$R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) with acetylacetone gave an imidazo[4,5-*b*]pyridine as the major product together with a small yield of the uncyclised N-adduct (**148**) (83JHC1015). Treatment of the 1,5-diaminoimidazoles (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$, CH_2Ph) with diacetyl gave the products (**149**; $R = \text{Ph}$) (80%) and (**149**; $R = \text{CH}_2\text{Ph}$) (74%), respectively [74BSF(2)1453].



(148)



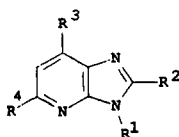
(149)

7. Formation of Bicyclic Heterocyclic Ring Systems

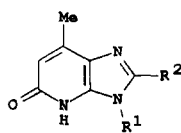
a. *Imidazo[4,5-*b*]pyridines*. Treatment of 1,5-diamino-2-phenylimidazole (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) with hot acetylacetone gave the imidazo[4,5-*b*]pyridine (**150**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{Me}$) (50%) and a low yield of the imidazo[1,5-*b*]-1,2,4-triazepine (**160**) (Section V,B,7,b). Similar treatment of the substituted imidazole (**96**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) gave the imidazo[4,5-*b*]pyridine (**150**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{Me}$) (40%) and a small amount of the condensation product (**148**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) (83JHC1015).

Heating a solution of 1,5-diamino-2-phenylimidazole (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) in ethanolic ethyl acetoacetate at reflux gave the imidazo[4,5-*b*]pyridone (**151**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) (75%) (78JHC937). The substituted imidazo[4,5-*b*]pyridone (**151**; $R^1 = \text{NHPh}$, $R^2 = \text{Ph}$) (80%) was similarly obtained. A hot acetic acid solution of the diaminoimidazole (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) when treated with the reagent (**162**; $R = \text{Me}$) gave the imidazo[4,5-*b*]pyridone (**152**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) (20%) in addition to the imidazo[1,5-*b*]triazepine (**161**; $R^1 = \text{Me}$, $R^2 = \text{Ph}$) (40%) (Section V,B,7,d) (78JHC937).

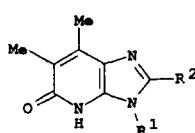
Recent studies have demonstrated the synthetic potential of 5-aminoimidazoles (**96**) as intermediates for heterocyclic synthesis, particularly for the synthesis of bicyclic systems, including imidazo[4,5-*b*]pyridines



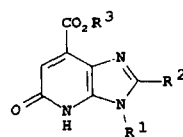
(150)



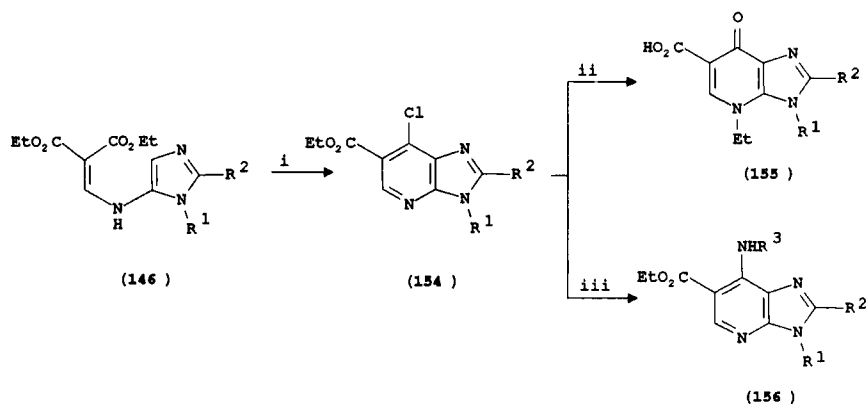
(151)



(152)



(153)

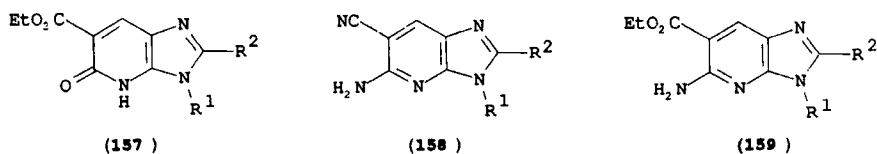


SCHEME 18. Reagents and conditions; (i) POCl_3 , heat, 7 h; (ii) 1 *M* NaOH, ethoxy ethanol, heat 3 h; EtI, heat, 1 h; EtOH, 1 *M* NaOH, heat, 0.5 h; (iii) H_2NR^3 , EtOH, heat, 7 h.

[92JCS(P1)2779, 92JCS(P1)2789]. Thermal cyclization of the adducts (129) and (130), formed by addition of 5-aminoimidazoles (96) to dialkyl acetylenedicarboxylates (Section V,B,5,c), was found to be facile and gave the imidazo[4,5-*b*]pyridones (153) [92JCS(P1)2779].

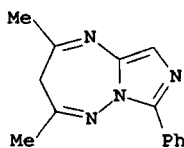
Treatment of the addition-elimination products (146), obtained in good yield from 5-aminoimidazoles (96) and diethyl ethoxymethylene-malonate (135) (Section V,B,6), with hot phosphoryl chloride gave the 7-chloroimidazo[4,5-*b*]pyridines (154), which have been used to prepare a wide range of derivatives, including the nalidixic acid analogues (155) and the cytokinin analogues (156) (Scheme 18) [92JCS(P1)2789].

The addition-elimination adducts (143)–(145) are also useful precursors to imidazo[4,5-*b*]pyridines. Thus, the malonate derived products (143) on treatment with hot ethanolic HCl [92JCS(P1)2789] or hot ethanolic triethylamine (78H241) gave the imidazo[4,5-*b*]pyridones (157). The dinitrile derivatives (144) gave the *ortho* amino nitriles (158) by treatment with hot methanolic sodium hydroxide solution and the nitrile esters (145)

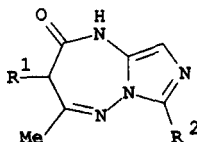


gave the amino esters (**159**) when heated under reflux in Thermex [92JCS(P1)2789].

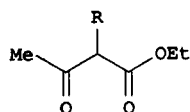
b. *Imidazo[1,5-b]-1,2,4-triazepines*. In addition to the imidazo[4,5-b]pyridine (**150**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) (Section V,B,7,a), the imidazo[1,5-b]-1,2,4-triazepine (**160**) (12%) was also obtained by treatment of 1,5-diaminoimidazole (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) with hot acetylacetone (83JHC1015). Imidazo[1,5-b]-1,2,4-triazepines (**161**; $R^1 = \text{H}$, $R^2 = \text{Ph}$) (80%) and (**161**; $R^1 = \text{Me}$, $R^2 = \text{Ph}$) (40%) were also obtained by treatment of hot acetic acid solutions of the diaminoimidazole (**96**; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) with the ethyl acetoacetate derivatives (**162**; $R = \text{H}$) and (**162**; $R = \text{Me}$), respectively (78JHC937). It should be noted that smaller amounts of the imidazo[4,5-b]pyridones (**151**) and (**152**) were obtained in these reactions (78JHC937).



(160)

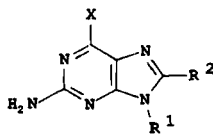


(161)

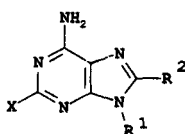


(162)

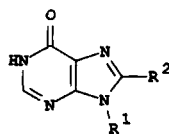
c. *Imidazo[4,5-c]pyrimidines (Purines)*. Incubation of AIR (106) with pigeon liver extract in the presence of sodium formate and glycine gave inosinic acid (**167**; $R^1 = \text{ribonucleotide}$, $R^2 = \text{H}$) in an estimated yield of 25% by using a ^{14}C -labeled atom (59BBA367). The products derived from the reaction of 5-aminoimidazoles (**96**) with ethoxymethyleneurethane (**138**), *S,S'*-dimethyl-*N*-cyanodithioiminocarbonate (**142**), ethyl *N*-cyanoformimidate (**139**), and the *N*-acylimidates (**140**) and (**141**) (Section V,B,6) provide the basis for a new synthesis of purines. Thus, facile thermal cyclization of the intermediates (**132**; $\text{Y} = \text{NCN}$, $R^3 = \text{H}$) and (**132**; $\text{Y} = \text{NCN}$, $R^3 = \text{SMe}$) gave the 2-aminopurines (**163**) and (**164**), whereas cyclization of the intermediates (**134**; $\text{Y} = \text{NCN}$, $R^3 = \text{H}$) and (**134**; $\text{Y} = \text{NCN}$, $R^3 = \text{SMe}$) provided a synthesis of adenine derivatives (**165**)



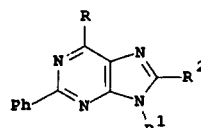
(163) $\text{X} = \text{H}$
 (164) $\text{X} = \text{SMe}$



(165) $\text{X} = \text{H}$
 (166) $\text{X} = \text{SMe}$



(167)

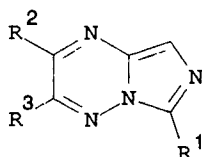


(168) $R = \text{Me}$, $R^1 = \text{NHPh}$
 (169) $R = \text{Et}$, $R^1 = \text{NHPh}$

and (166), respectively. Thermal cyclization of the urethane derivatives (134; $Y = \text{NCO}_2\text{Et}$, $R^3 = \text{H}$) provided the novel hypoxanthine derivatives (167; $R^1 = \text{alkyl}$, $R^2 = \text{H}$, alkyl) [92JCS(P1)2789] and other analogues have been obtained by this method (85M11).

The N-adducts derived by reaction of 1,5-diaminoimidazoles (96; $R^1 = \text{NHPh}$, $R^2 = \text{aryl}$, $i\text{Pr}$) with the *N*-acylimidates (140) and (141) were cyclized smoothly in hot xylene solution to give the corresponding purines (168) and (169) in good yield (85M11).

d. *Imidazo[1,5-*b*]-1,2,4-triazines*. Treatment of a boiling solution of 1,5-diamino-2-phenylimidazole (96; $R^1 = \text{NH}_2$, $R^2 = \text{Ph}$) in acetonitrile containing diacetyl gave the imidazo[1,5-*b*]-1,2,4-triazine (170; $R^1 = \text{Ph}$, $R^2 = R^3 = \text{Me}$) (25%) after purification by chromatography. Similarly, the benzyl analogue (170; $R = \text{CH}_2\text{Ph}$, $R^2 = R^3 = \text{Me}$) (20%) was obtained from the imidazole (96; $R^1 = \text{NH}_2$, $R^2 = \text{CH}_2\text{Ph}$) and diacetyl [74BSF(2)1453].

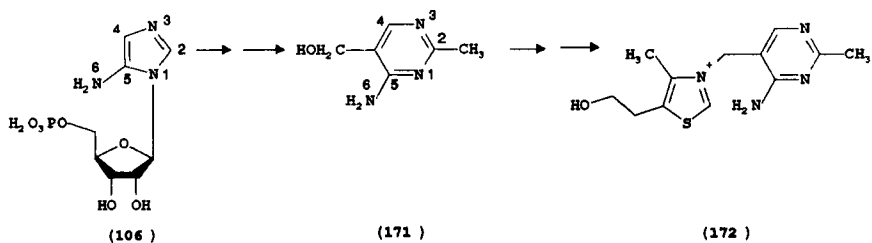


(170)

8. Miscellaneous Reactions

It has been demonstrated that AIR (106) is an intermediate in the biosynthesis of thiamine (vitamin B_1), (172) (68BJ279; 69BBA375; 70BBA170; 82M13; 83M13; 84JA3857). The higher plants, a number of fungi, and most bacteria can synthesize thiamine (172). It has been demonstrated using ^{13}C - and ^{14}C -labeling experiments with *Salmonella typhimurium* that all the carbon atoms in the pyrimidine moiety of thiamine (172) are derived from AIR (106) (84JA3857). It was concluded that the atoms (both C and N) from the imidazole nucleus of AIR (106) were incorporated into the intermediate pyrimidine (171) as indicated by the numbering of the respective atoms (Scheme 19). In the intermediate (171) there remain three carbon atoms not designated and these were shown to be derived from the ribonucleotide residue of AIR (106) (82M13; 84JA3857).

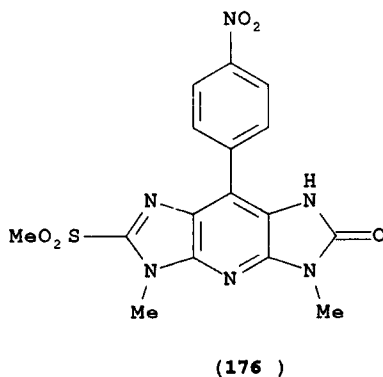
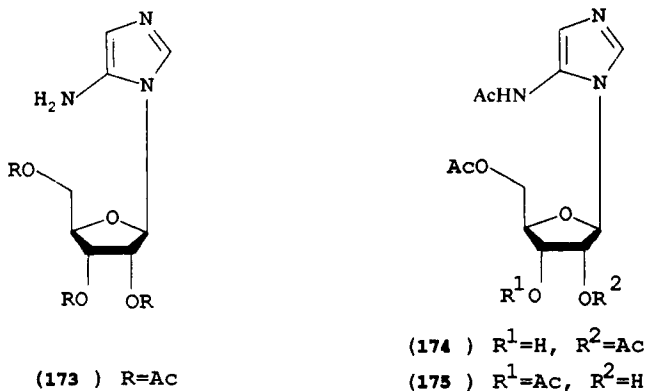
The tri-*O*-acetyl derivative of 5-amino-1-(β -D-ribofuranosyl)imidazole (173) has been found to undergo a facile rearrangement at pH 7 to give a mixture of the 5-acetamido derivatives (174) and (175) (90JA4891). The transacetylation was quite rapid ($t_{1/2} = 15\text{h}$), but the authors noted that it proceeded more slowly at both higher and lower pH. An earlier report



SCHEME 19

by the same authors (88PNA7174) that this rearrangement (**173** → **174** + **175**) was a Dimroth-type rearrangement of the aminoimidazole has been corrected (90JA4891).

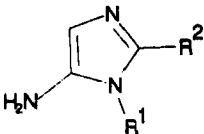
Treatment of an ethyl acetate solution of the 5-aminoimidazole (**96**; $R^1 = \text{Me}$, $R^2 = \text{SO}_2\text{Me}$) with *p*-nitrobenzaldehyde in the presence of trifluoroacetic acid gave a crystalline product, which was assigned the tricyclic structure (**176**) on the basis of spectral data [82IJC(B)1087].



C. LITERATURE SURVEY

Table VI summarizes 5-aminoimidazole derivatives (96), which have been described as the free base or as a simple salt, or have been generated *in situ* and used immediately without isolation.

TABLE VI
KNOWN 5-AMINOIMIDAZOLE DERIVATIVES (96)

 (96)					
R ¹	R ²	Free base	Salt	<i>In situ</i>	Reference
Me	SH	✓	—	—	48JCS2028
Me	COPh	✓	—	—	82IJC(B)1087
Me	SO ₂ Me	✓	—	—	82IJC(B)1087
NH ₂	Ph	✓	—	—	74BSF(2)1453; 78JHC937
NHPh	Ph	✓	—	—	74BSF(2)1453; 78JHC937
NH ₂	CH ₂ Ph	✓	—	—	74BSF(2)1453
NHPh	CH ₂ Ph	✓	—	—	74BSF(2)1453
Me	Me	✓	—	—	92JCS(P1)2779; 89CC551
Me	Me	—	Picrate	—	59JCS1648
Me	Me	—	HCl	—	87MI2
Me	H	✓	—	—	92JCS(P1)2779
Me	H	—	Picrate	—	59JCS1648; 48JCS2028
CH ₂ CH ₂ OH	Me	✓	—	—	92JCS(P1)2779; 89CC551
CH ₂ CH ₂ OH	Me	—	HCl	—	87MI1
Me	<i>i</i> Pr	—	—	✓	92JCS(P1)2779
Me	CH ₂ CH ₂ Ph	—	—	✓	92JCS(P1)2779
C ₆ H ₁₁	H	—	Picrate	—	66JCS(C)2270
C ₆ H ₁₁	Me	—	Picrate	—	71JCS(C)1501
Et	H	—	Picrate	—	59JCS1648
2-Pyridyl	H	—	Picrate	—	80JCS(P1)2316
Amlodipinyl	OH ^a	—	HCl	—	90JMC1805
NH ₂	H	—	Picrate	—	61JCS4845
NHPh	4-Me-C ₆ H ₄	—	—	✓	85MI1
NHPh	Ph	—	—	✓	85MI1
NHPh	3-Me-C ₆ H ₄	—	—	✓	85MI1
NHPh	CH ₂ Ph	—	—	✓	85MI1
NHPh	4-Cl-C ₆ H ₄	—	—	✓	85MI1
NHPh	<i>i</i> Pr	—	—	✓	85MI1
β-D-Ribofuranosyl	H	✓	—	—	88PNA7174; 90JA4891
Triacetyl-β-D-ribofuranosyl	H	✓	—	—	88PNA7174; 90JA4891
β-D-Ribofuranosyl phosphate	H	—	NH ₄ ⁺	—	90JA4891
D-Galactosyl	Me	—	Picrate	—	59JCS1648

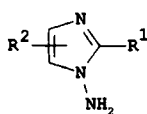
^a This example exists as the oxo tautomer.

VI. Physical Properties and Theoretical Studies of Aminoimidazoles

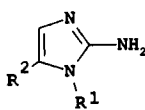
A. SPECTROSCOPIC METHODS

1. ^1H NMR Spectroscopy

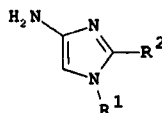
All of the regioisomeric aminoimidazoles [when studied as the free bases, i.e., (177–180)] have been shown to exist as amino tautomers in solution by ^1H NMR spectroscopy. Typical chemical shifts for the broad singlet signals corresponding to the protons of the NH_2 groups are given in Table VII. Chemical shifts of the C4- and C5-protons are also given. In all cases where an amino group occupies the *ortho* C5- or C4- position, the chemical shift of the C4-H or C5-H is shifted considerably upfield. In the case of compound (180; $\text{R}^1 = \text{CH}_2\text{CH}_2\text{OH}$, $\text{R}^2 = \text{Me}$), it was concluded



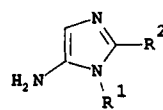
(177)



(178)



(179)



(180)

TABLE VII
CHEMICAL SHIFTS OF NH_2 GROUPS OF TYPICAL AMINOIMIDAZOLES^a

Compound	R^1	R^2	Chemical shift of NH_2 (δ)	Chemical shift of C5-H or C4-H (δ)	Reference
177	Ph	5- NH_2	5.50	6.1 (C4-H)	78JHC937
177	SMe	5-Ph	4.55 ^b	7.00 ^b (C4-H)	78BCJ1846
177	SMe	4-Ph	4.70 ^b	Not recorded	78BCJ1846
178	2-PhO-C ₆ H ₄	H	5.22	6.43 and 6.63	85CPB4409
178	Me	H	5.10	6.5 (two signals)	80JHC337
179	Me	$\text{CO}_2\text{CH}_2\text{Ph}$	3.58 ^b	6.34 ^b (C5-H)	90ACS(B)67
179	Me	CO_2Et	3.69 ^b	6.37 ^b (C5-H)	90ACS(B)67
180	β -D-Ribofuranosyl	H	not observed ^c	6.34 ^c (C4-H)	90JA4891
180	NH_2	Ph	4.56	6.1 (C4-H)	78JHC937
180	NH_2	CH_2Ph	4.75	6.02 (C4-H)	74BSF(2)1453
180	NHPh	Ph	4.45	6.35 (C4-H)	78JHC937
180	Me	H	4.50	6.2 (C4-H)	92JCS(P1)2779
180	Me	Me	4.15	5.8 (C4-H)	92JCS(P1)2779
180	$\text{CH}_2\text{CH}_2\text{OH}$	Me	4.06	5.95 (C4-H)	92JCS(P1)2779

^a Determined by hexadeuterodimethyl sulfoxide unless stated otherwise.

^b Determined in deuteriochloroform.

^c Determined in D_2O .

that the amino group *shields* the C4-proton about as effectively as the nitro group in metronidazole, (**97**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) *deshields* the C4-proton (82MI1).

2. ^{13}C and ^{15}N NMR Spectroscopy

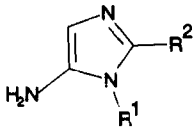
No ^{13}C spectral data are available for 4-aminoimidazoles (**179**), but the ^{13}C spectra of four 5-aminoimidazoles (**180**) have been reported. Typical chemical shifts for the C5 and C4 atoms are recorded in Table VIII.

The ^{15}N NMR spectra has been recorded for 5-aminoimidazole ribonucleotide (**180**; $R^1 = \beta\text{-D-Ribofuranosyl}$; $R^2 = \text{H}$). The NH_2 group was observed at a chemical shift of $\delta\text{-354.5}$ (nitromethane as internal standard) (90JA4891).

3. Ultraviolet Spectroscopy

The UV spectra of several 5-aminoimidazoles (**180**) have been examined in ethanol or acetonitrile solution (Table IX). A change of pH from neutral to either basic or acidic pH results in a shift of maxima. For example, compound (**180**; $R^1 = R^2 = \text{Me}$) in ethanolic solution with 1 *M* HCl gave two maxima at 210 nm (ϵ 1470) and 243 nm (ϵ 2040), and in ethanolic solution with 1 *M* NaOH gave one maxima at 216 nm (ϵ 10720) (87TH1). Also, AIRs (**180**; $R^1 = \text{ribonucleoside}$, $R^2 = \text{H}$) displayed a single maxima

TABLE VIII
CHEMICAL SHIFTS OF THE C5 AND C4 CARBON ATOMS OF 5-AMINOIMIDAZOLES (**180**)^a

 (180)					
Compound	R^1	R^2	Chemical shift of C5 (δ)	Chemical shift of C4 (δ)	Reference
180	$\beta\text{-D-Ribofuranosyl}$	H	135.4 ^b	112.1 ^b	88PNA7174
180	Triacetyl- $\beta\text{-D-ribofuranosyl}$	H	134.9 ^c	114.9 ^c	88PNA7174
180	Me	Me	139.09	112.5	92JCS(P1)2779
180	$\text{CH}_2\text{CH}_2\text{OH}$	Me	139.22	111.07	92JCS(P1)2779

^a Determined in pentadeuteropyridine unless stated otherwise.

^b Determined in D_2O .

^c Determined in deuteriochloroform.

TABLE IX
ULTRAVIOLET SPECTRAL DATA FOR 5-AMINOIMIDAZOLES (180)

(180)

Solvent	R ¹	R ²	λ_{\max} (nm)	ϵ	Reference
EtOH	Me	Me	221	2440	92JCS(P1)2779
EtOH	CH ₂ CH ₂ OH	Me	221	5550	92JCS(P1)2779
EtOH	CH ₂ CH ₂ OH	Me	215	5000	82MI1
MeCN	NH ₂	Ph	215, 300	7240, 10470	74BSF(2)1453
H ₂ O (pH 7)	Ribofuranosyl	H	214	4500	90JA4891
H ₂ O (pH 7)	Tri- <i>O</i> -acetyl Ribofuranosyl	H	213	4400	88PNA7174

in aqueous media at pH 1 at 210 nm (ϵ 4600) and a single maxima at pH 11 at 234 nm (ϵ 3700) (90JA4891).

4. Infrared Spectroscopy

The solid-state IR spectra (KBr discs) have been recorded for several simple 5-aminoimidazoles (**180**; R¹, R²=alkyl) and are consistent with these compounds existing as amino tautomers (92JCS(P1)2779). Typically, the two NH stretching frequencies of the amino group are observed between 3300 and 3400 cm⁻¹. The frequencies of the NH deformations are observed in the range 1590–1615 cm⁻¹.

5. Mass Spectrometry

Little information on the mass spectral behavior of aminoimidazoles has been reported. High-resolution fast-atom bombardment (FAB) was used as a means of obtaining accurate mass data for the ribofuranosyl derivatives (**180**; R¹ = triacetyl- β -D-ribofuranosyl, β -D-ribofuranosyl, R² = H) (88PNA7174; 90JA4891). Using electron impact mass spectrometry limited fragmentation was observed for the 5-aminoimidazole (**180**; R¹ = R² = Me): in addition to the molecular ion (m/z 111, 100%), fragment ions corresponding to $M^{\cdot+} - \text{Me}$ (m/z 96), $M^{\cdot+} - 2\text{Me}$ (m/z 81), and $M^{\cdot+} - (\text{Me and NH}_2)$ (m/z 80) were observed. A fragment at m/z 70 was also observed, which probably arises from ring cleavage and loss of acetonitrile

(87UP1). Similar fragmentation was observed for the aminoimidazole (**180**; $R^1 = \text{CH}_2\text{CH}_2\text{OH}$, $R^2 = \text{Me}$) (82MI1).

B. MOLECULAR GEOMETRY

Structure determinations of simple 4- and 5-aminoimidazoles (**179**) and (**180**) by X-ray crystallography have not been reported. However, derivatives of AIR (**180**; $R^1 = \text{ribonucleotide}$, $R^2 = \text{H}$) bearing substituents at the 4-position of the imidazole have been examined by X-ray crystallography and in these examples, the amino groups were found to be slightly pyramidal with bond lengths in the range 1.343–1.359 Å [79AX(B)924; 90AX(C)2205]. Similarly, the structures of several 2-aminoimidazoles have been determined [87AX(C)507; 88AX(C)1816; 90AX(C)1295; 91AX(C)337]. In the case of the picrate salts of the 2-aminoimidazoles, when the imidazole ring was protonated, the amino groups were found to be slightly pyramidal with bond lengths in the range 1.311–1.331 Å [87AX(C)507]. In the case of the 2-aminoimidazole free bases, the amino groups were found to be almost planar and typically in the range 1.359–1.361 Å [88AX(C)1816; 90AX(C)1295] but a shorter bond length was observed (1.333 Å) when the imidazole ring was substituted with powerful electron-withdrawing substituents (two nitrile groups) [91AX(C)337].

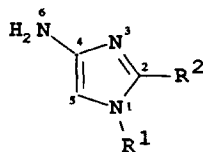
Using the semiempirical AM1 method with full structure optimization, the bond lengths and bond angles of 4- and 5-aminoimidazoles (**179**) and (**180**) have been calculated [92JCS(P1)2779] and the results are summarized in Table X.

C. MOLECULAR ORBITAL CALCULATIONS

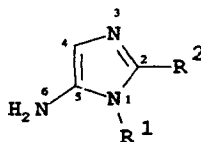
Using the INDO approximation on fully optimized geometries, the lone pair orbital energy (ϵ_N) (of 3-*N*) in 4-aminoimidazole (**179**; $R^1 = R^2 = \text{H}$) was calculated to be 0.4482 au and the protonation energy (ΔE_p) of the same molecule was calculated to be 374.9 kcal mol⁻¹ (83H1717).

Using a semiempirical SCF MO π approximation, the tautomerism of several amino heterocycles has been studied (70JA2929). From the theoretical heats of atomization of the tautomers of 4-aminoimidazole (**181a–d**), it was suggested that there would be a slight predominance of 1-*H*-4-

TABLE X
AM1 CALCULATED GEOMETRIES OF 4- AND 5-AMINOIMIDAZOLES (179) AND (180)



(179)



(180)

Geometrical parameters

Molecule	Bond lengths (XY, Å)						Bond angles (XYZ, degrees) ^a				
	N ¹ C ²	C ² N ³	N ³ C ⁴	C ⁴ C ⁵	N ¹ C ⁵	C ⁴ N ⁶ or C ⁵ N ⁶	N ¹ C ² N ³	C ² N ³ C ⁴	N ³ C ⁴ C ⁵	N ¹ C ⁵ C ⁴	C ⁵ C ⁴ N ⁶ or C ⁴ C ⁵ N ⁶
179 (R ¹ = R ² = H)	1.396	1.348	1.417	1.420	1.395	1.403	112.1	105.3	109.4	106.1	125.3
179 (R ¹ = R ² = Me)	1.406	1.357	1.416	1.419	1.396	1.404	111.4	105.5	109.6	106.2	125.2
180 (R ¹ = R ² = H)	1.404	1.346	1.391	1.422	1.413	1.401	111.8	106.3	109.9	105.7	128.7
180 (R ¹ = R ² = Me)	1.419	1.355	1.388	1.421	1.414	1.402	111.1	106.6	110.2	105.9	127.9

^a The amino groups were calculated to be pyramidal.

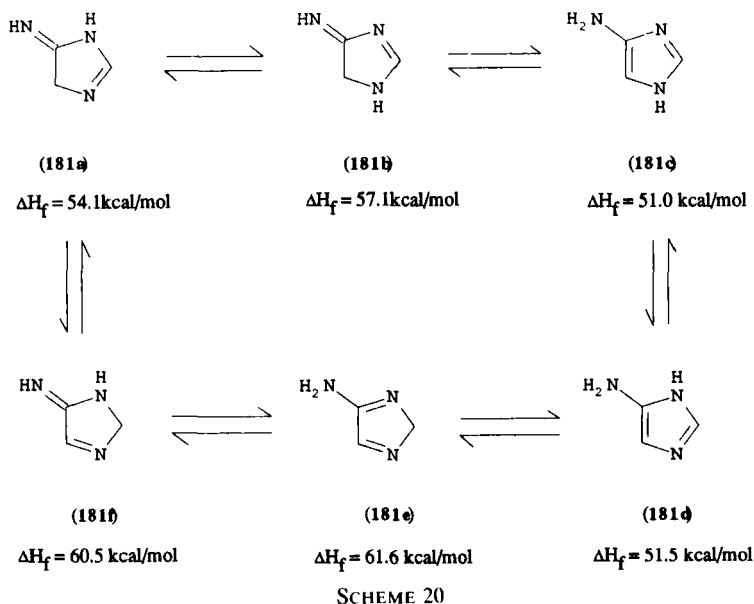


TABLE XI
AM1 CALCULATED CHARGE DISTRIBUTION (e) AND FRONTIER ORBITAL ENERGIES (E)
AND COEFFICIENTS FOR 4- AND 5-AMINOIMIDAZOLES (**179**) AND (**180**)

Compound	(179)			(180)			
	E/eV	N-1	C-2	N-3	C-4	C-5	N-6
179 ; $R^1 = R^2 = \text{H}$:	e/au	—	-0.21	-0.09	-0.17	-0.04	-0.21
	HOMO	-8.38	-0.25	-0.38	0.06	0.45	0.57
	LUMO	1.02	-0.44	0.54	-0.22	-0.35	0.57
179 ; $R^1 = R^2 = \text{Me}$:	e/au	—	-0.15	-0.03	-0.17	-0.04	-0.20
	HOMO	-8.16	-0.28	-0.40	0.03	0.45	0.56
	LUMO	0.99	-0.42	0.55	-0.26	-0.30	0.53
180 ; $R^1 = R^2 = \text{H}$:	e/au	—	-0.23	-0.11	-0.12	-0.22	-0.02
	HOMO	-8.38	-0.01	-0.49	-0.18	0.53	0.48
	LUMO	0.92	0.40	-0.49	0.20	0.34	-0.60
180 ; $R^1 = R^2 = \text{Me}$:	e/au	—	-0.18	-0.06	-0.12	-0.22	-0.02
	HOMO	-8.15	0.03	0.49	0.21	-0.51	-0.48
	LUMO	0.88	0.38	-0.49	0.22	0.30	-0.57

aminoimidazole (**181c**) in the equilibrium (**181a**) \rightleftharpoons (**181b**) \rightleftharpoons (**181c**) \rightleftharpoons (**181d**) (70JA2929).

Later studies using the AM1 method with full structure optimization calculated the same order of stability of the tautomers (**181a–d**) with the 2-*H*-imidazole tautomers (**181e,f**) being calculated to be considerably less stable (Scheme 20) [92JCS(P1)2779]. Thus, 1-*H*-4-aminoimidazole (**181c**) was calculated to be most stable ($\Delta H_f = 51$ kcal/mol), and the diazacyclopentadiene (**181e**) was least stable ($\Delta H_f = 61.6$ kcal/mol). However, the energy difference between the 4-amino (**181c**) and the 5-amino (**181d**) tautomers is very small. Furthermore, the calculated dipole moments of the two tautomers (**181c**) and (**181d**) are similar (3.22 D and 4.02 D, respectively), unlike the corresponding nitroimidazoles, and thus the polarity difference between the tautomers (**181c** \rightleftharpoons **181d**) is small [92JCS(P1)2779]. If, as suggested for nitroimidazoles (89CJC1666, 89MI2), the degree of solvent stabilization is related to the size of the dipole moment, the solvent stabilization of the two tautomers (**181c**) and (**181d**) can be expected to be similar. Thus, since the calculated energy difference

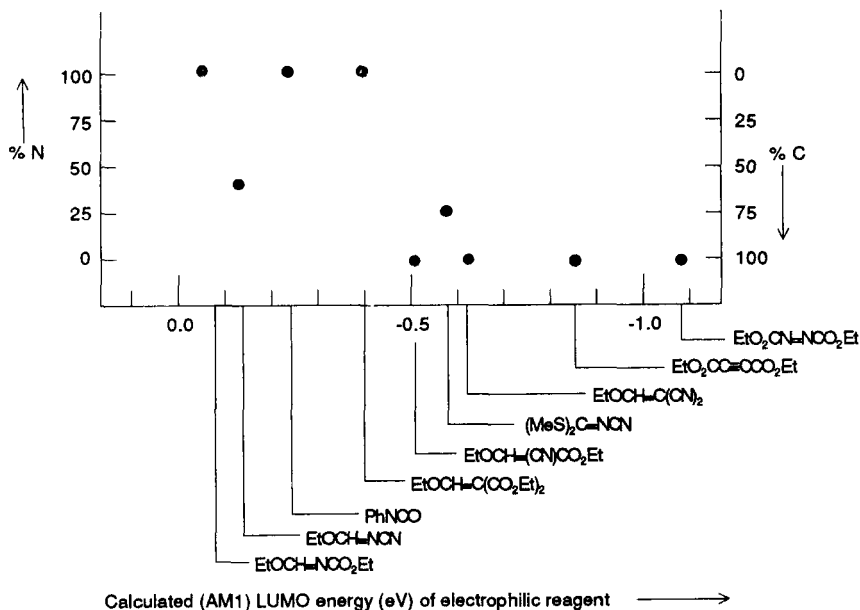


FIG. 1. Relative yields of C- and N-adducts from the reaction of 5-amino-1,2-dimethylimidazole with various electrophilic reagents. (Adapted from the original [92JCS(P1)2789] by kind permission of the Royal Society of Chemistry.)

between the tautomers (**181c**) and (**181d**) in the gas phase is small, both tautomers (**181c**) and (**181d**) can be predicted to be present in solution.

The charge distribution and frontier orbital energies and coefficients have been calculated for 4- and 5-aminoimidazoles (**179**) and (**180**) using the AM1 method [92JCS(P1)2779] and the results are summarized in Table XI.

The aminoimidazoles (**179**) and (**180**) can in principle react with electrophilic reagents by either N- or C-addition. In earlier sections it can be seen that the type of addition or addition-elimination product arising from the reactions of 4- and 5-aminoimidazoles with various reagents varies depending on the nature of the reagent. Using molecular orbital studies, Ramsden and co-workers have concluded that C-addition to 5-aminoimidazoles is favored by soft electrophiles, whereas N-addition is favored by hard electrophiles [92JCS(P1)2789]. This is illustrated in Fig. 1, which shows the relative experimental yields of C-adducts and N-adducts arising from reactions of 5-aminoimidazoles with various reagents plotted against the calculated LUMO energies of the reagents. From Fig. 1 it can be seen

TABLE XII
AM1 CALCULATED PROPERTIES OF SOME ELECTROPHILIC REAGENTS AND
RELATED SPECIES

Species	LUMO energy (eV)	LUMO coefficient on reacting atom ^a	Total charge on reacting atom ^a
(HO) ₂ CO	1.06	0.80	+0.40
CO	0.94	0.86	+0.20
CO ₂	0.85	0.80	+0.41
EtOCH = CHCO ₂ Et	0.18	0.67	+0.06
HC = CCO ₂ Et	0.14	0.57	-0.10
EtOCH = NCO ₂ Et	-0.08	0.68	+0.12
EtOCH = NCN	-0.14	0.71	+0.11
PhNCO	-0.24	0.40	+0.33
EtOCH = C(CO ₂ Et) ₂	-0.40	0.72	+0.13
EtOCH = C(CN)CO ₂ Et	-0.51	0.72	+0.11
2-Me-4-nitroimidazole	-0.57	0.59 ^b	-0.06 ^b
(MeS) ₂ C = NCN	-0.58	0.70	-0.22
EtOCH = C(CN) ₂	-0.62	0.72	+0.09
EtO ₂ C · C ≡ C · CO ₂ Et	-0.85	0.42	-0.07
2-Me-5-nitroimidazole	-1.02	0.42 ^c	-0.04 ^c
EtO ₂ C · N = N · CO ₂ Et	-1.08	0.40	-0.01

^a The reacting atom is defined as that at which new bond formation occurs and is indicated in italics.

^b The reacting atom is the carbon at position 5.

^c The reacting atom is the carbon at position 4.

that softer electrophilic reagents (i.e., lower LUMO energy) favor the formation of C-adducts.

The calculation of the preferred mode of addition (N or C) of electrophilic species to 5-aminoimidazoles was extended to include other species (Table XII) from which several conclusions were drawn: (a) reagents with a calculated (AM1) LUMO energy > 0 eV do not readily undergo electrophilic additions to the aminoimidazoles; (b) reagents with a calculated (AM1) LUMO energy in the range $0 \text{ eV} > \text{LUMO} > -0.5 \text{ eV}$ react predominantly on the exocyclic nitrogen atom; (c) reagents with a calculated (AM1) LUMO energy $< -0.5 \text{ eV}$ react predominantly on the C-4 of the imidazole. It was also noted that the low LUMO energy of the nitroimidazoles (Table XII) provides a rationalization for the formation of dehydro dimers (33) during catalytic hydrogenation of certain nitroimidazoles (Section III,A,1; III,B,5), i.e., the nitroimidazole precursor behaves as a soft electrophile and undergoes C-addition to the aminoimidazole.

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Phosphorus Heterocycles from α -Hydroxyalkylphosphines and Vinylphosphines

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I. Introduction

Interest in phosphorus-containing heterocycles results from a consideration of their purely theoretical aspects (conformational analysis, tautomerism, donor–acceptor interactions), and also from their continuously increasing importance in the synthesis of new catalysts, biologically active compounds, etc. Of great interest are heterocyclic structures with heteroatoms and heteroatomic functional groups in a 1,3-position. Significant interactions were shown to be present in such systems, essentially influencing their properties. Functionally substituted phosphines are convenient precursors for the synthesis of such heterocyclic systems. 1,3,2-Dioxaphosphorinanes, 1,3,5-diazaphosphorinanes, 1,3,2,5-dioxasilaphosphorinanes, 1,3,2,5-dioxaboraphosphorinanes, 1,5,3,7-diazadiphosphacyclooctanes, and some other heterocyclic compounds have been obtained on this basis. The properties of such heterocyclic systems have been partially discussed in reviews [63HOU28; 72MI2; 81MI1; 83MI1; 84MI1, 84UK625, 84ZC365; 86MI1; 90MI1, 90PS(49-50)271; 92UK616]. In this survey we mainly present the results of recent studies concerning the chemistry of heterocyclic systems.

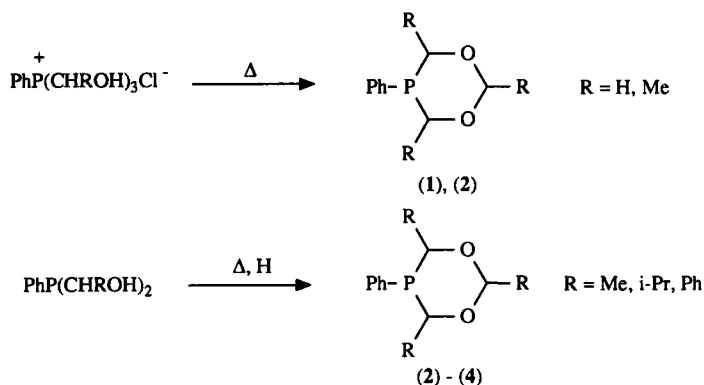
II. Heterocycles with P—C—O Fragments

A. SYNTHESIS

1. 1,3,5-Dioxaphosphorinanes

An extensive investigation of the synthesis of 1,3,5-dioxaphosphorinanes was carried out by Buckler (61JA168, 61USP2984683, 61USP3005020). These were obtained from phosphorus-containing diols and aldehydes and from phosphines and aldehydes. B. A. Arbuzov and co-workers carried out systematic investigations of heterocycles with $P(—CHR—X)_2$ fragments, where X is a nitrogen or oxygen atom [83MI1; 84MI1, 84UK625; 86MI1; 90MI1, 90PS(49-50)271; 92UK616].

α -Hydroxyalkylphenylphosphine (79IZV866; 80IZV1626) and phenylphosphine derivatives (80IZV1626) disproportionate to form 1,3,5-dioxaphosphorinanes (1)–(4) [Eq. (1)]. The ease of disproportionate depends on the coordination of the phosphorus atom and on the nature of substituents at carbon atoms bonded to it.

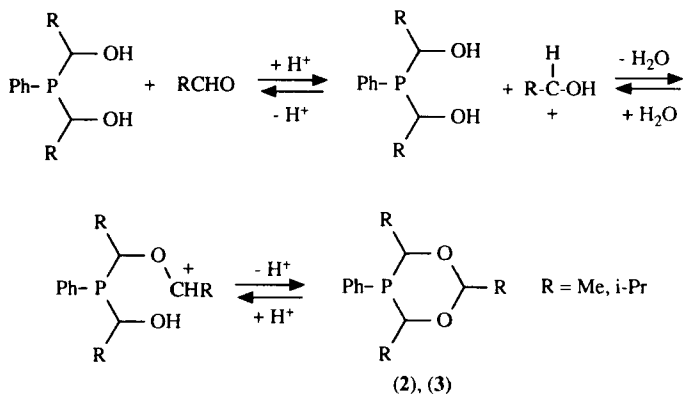


1,3,5-Dioxaphosphorinanes with R = *i*-Pr (3) and Ph (4) have also been obtained from phosphorus-containing diols and aldehydes [79IZV2136, 79DOK(244)610]. Phosphorus-containing diols with P(III) are very labile and are capable of dissociation and disproportionation under the reaction conditions. This apparently explains the difference in the physical constants of diols obtained by different authors.

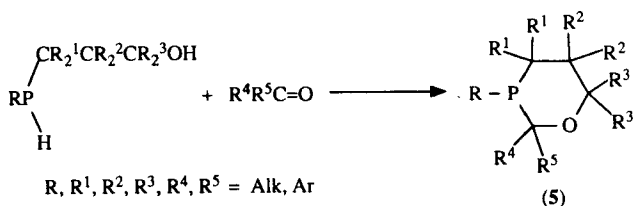
α -Hydroxyalkyl derivatives of phenylphosphine contain two asymmetric carbon atoms and exist as a mixture of *d,l* and *meso* forms. With aldehydes, they can form products of both kinetic and thermodynamic control. In the reaction of bis(α -hydroxyalkyl)phenylphosphines with aldehydes, products of kinetic control are initially formed; after that an equilibrium of stereoisomers is established. The stereoisomeric composition of the products of kinetic control differs sharply from that of the products of thermodynamic control and is similar to the ratio of *d,l* and *meso* forms in the starting diols [79DOK(244)610]. Reactions proceed via the formation of a carbocation with a positive charge at the carbon atom bonded to oxygen [Eq. (2)].

2. 1,3-Oxaphosphorinanes

Issleib, Oehme, and Zschunke [72MI1; 73ZC(13)291; 78PS(5)81; 79ZC57] obtained secondary phosphines with a γ -oxypropyl substituent via the addition of primary phosphines to allyl alcohols and studied their reactions with aldehydes and ketones. Addition of carbonyl compounds proceeds without catalysts at room temperature and is accompanied by

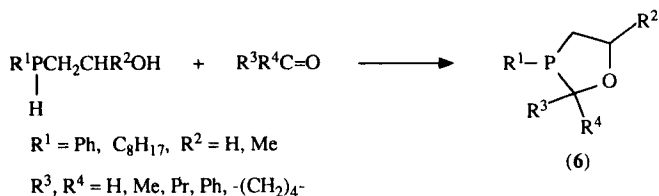


the formation of water. The reaction gives 1,3-oxaphosphorinanes (5) possessing different substituents in the ring [Eq. (3)].



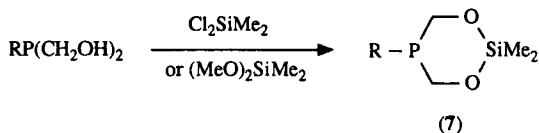
3. 1,3-Oxaphospholanes

Secondary phosphines with a β -hydroxyethyl substituent, obtained by addition of primary phosphines to α -oxides, easily undergo a reaction with ketones and aldehydes, giving 1,3-oxaphospholanes (6) [Eq. (4)] (72T2587).

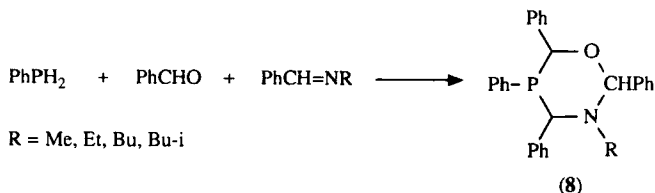


4. Miscellaneous Heterocycles

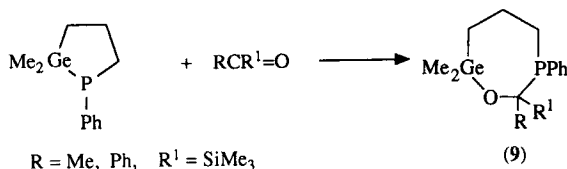
The introduction of dimethyldichlorosilane and dimethoxysilane into the reaction with alkylbis(oxymethyl)phosphines led to the formation of 1,3,2,5-dioxasilaphosphorinanes (7) [Eq. (5)] [79DOK(247)609].



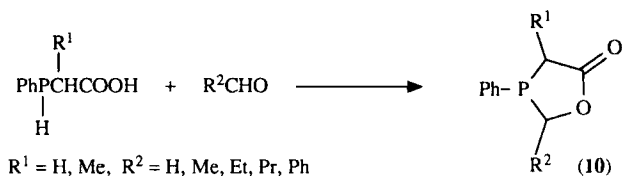
Successive addition of phosphine to an aldehyde and then reaction with an azomethine gives 1,3,5-azoxaphosphorinanes (**8**) (74MI1) possessing both P—C—O and P—C—N fragments [Eq. (6)].



One of the possible synthetic ways to obtain heterocyclic phosphines is the insertion of carbonyl compounds into the P—E (E = Si, Ge) bond of sila- and germa-phospholanes. Thus, the enlargement of the ring takes place and the P—C—O—E fragment is formed (**9**) [Eq. (7)] (74MI1; 75JOMC35; 77JOM35). The heterocyclic phosphepanes are obtained as a mixture of stereoisomers.

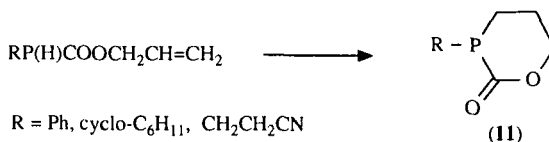


The interaction of carboxyalkylphosphines with aldehydes belongs to the same type of reactions reported above. The phenyl-(α -hydroxyalkyl)-carboxyalkylphosphine products transform into phosphorus-containing lactones (**10**) and water [Eq. (8)] [72JPR66; 73ZC(13)310].

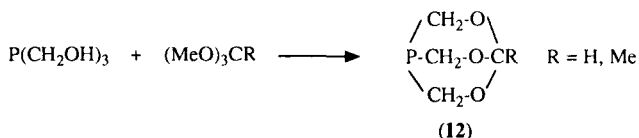


Intermolecular cyclization of allyloxycarbonylphosphines in the presence of azabisobutyronitrile also results in the formation of heterocycles containing the P—C—O fragment (**11**) [Eq. (9)] (82ZN965).

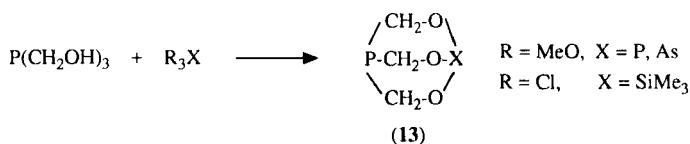
Several bicyclic compounds with the P—C—O fragments, which can be obtained from tris(oxyethyl)phosphine, are known. Thus, the interaction



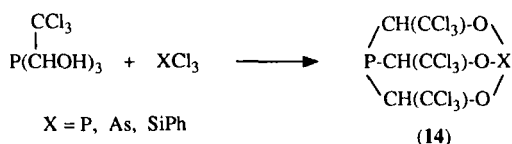
with orthoformate leads to the formation of **12** [Eq. (10)] (66JA1140; 80ZOB2424).



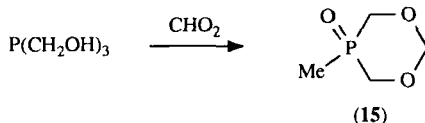
Bridged bicycles (**13**), containing different elements, were synthesized using tris(hydroxymethyl)phosphine [Eq. (11)] (65IC1655; 70JOC2310; 73PS1).



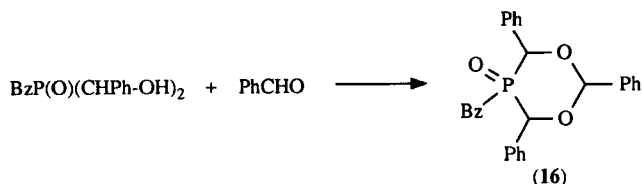
Tris(α -hydroxy- β,β,β -trichloroethyl)phosphine reacts with phenyl-trichlorosilane, phosphorus, and arsenic trichlorides in the same way, giving bicyclic product (**14**) [Eq. (12)] (78ZOB2437).



Heterocycles with the P—C—O fragment can be obtained by rearrangement of functionally substituted phosphines. For example, tris(hydroxyethyl)phosphine isomerizes into 5-methyl-5-oxo-1,3,5-dioxaphosphorinane (**15**) in the presence of formaldehyde [Eq. (13)] (78ZOB2653).

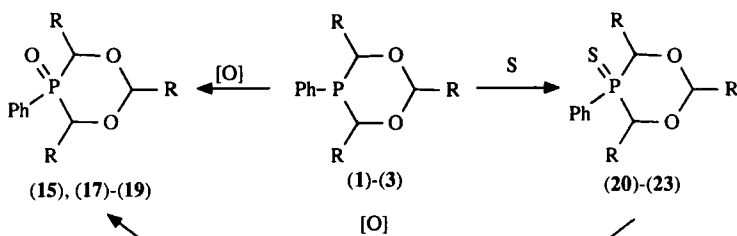


1,3,5-Dioxaphosphorinane oxide (**16**) is formed by interaction of benzaldehyde with benzylbis(α -hydroxybenzyl)phosphine oxide [Eq. (14)] on prolonged heating in the presence of an acidic catalyst (75JOC2056).

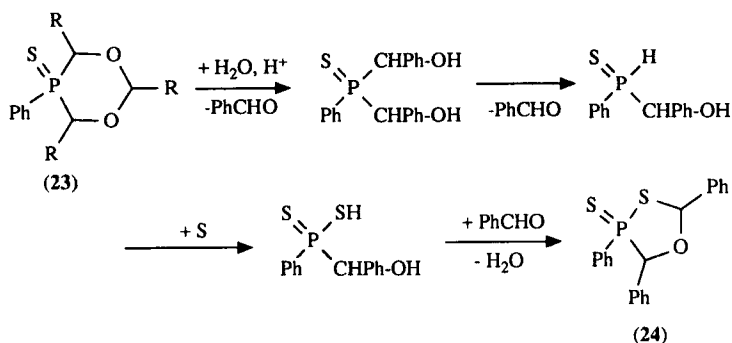


B. REACTIONS

1,3,5-Dioxaphosphorinanes (1)–(3) readily oxidize and add sulfur and selenium [78IZV1911; 79DOK(244)610, 79IZV866, 79IZV2136, 79IZV2239; 80IZV1626, 80IZV1630; 82IZV127]. The oxides have also been obtained by oxidation of the sulfides with hydrogen peroxide [Eq. (15)]. Oxidation, addition of sulfur, and replacement of sulfur by oxygen proceed stereospecifically, with retention of configuration at the phosphorus atom.

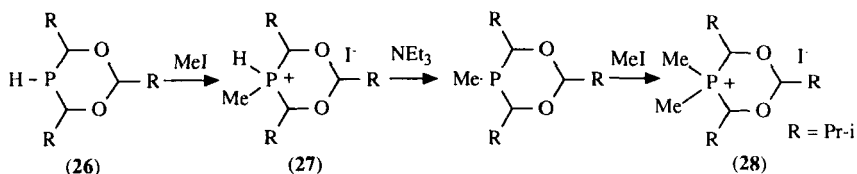


An interesting conversion was observed when 5-thiono-2,4,5,6-tetraphenyl-1,3,5-dioxaphosphorinane (**23**) was refluxed in benzene in an acidic medium (79IZV2136) with excess sulfur. 3-Thio-2,3,5-triphenyl-1,4,3-oxathiaphospholane (**24**) was formed. The following reaction mechanism may be proposed [Eq. (16)]. In favor of this mechanism is the fact

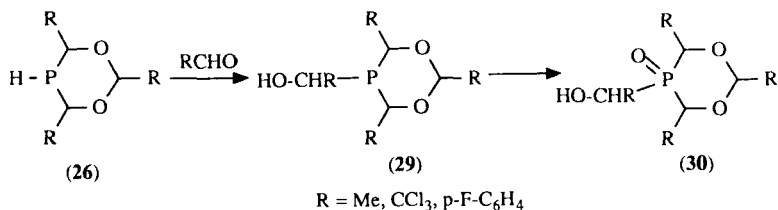


that oxathiaphospholane (**24**) has been obtained by heating bis(hydroxybenzyl)phenylphosphine with sulfur at 120–130°C.

5-Methyl-2,4,6-triisopropyl-1,3,5-dioxaphosphorinanes (**27**) have been obtained by the addition of methyl iodide to (**26**) (79IZV1863). The alkylation did not stop at the first stage. Together with the product of the addition of one molecule of methyl iodide, a product of dialkylation (**28**) was also obtained [Eq. (17)]. The addition proceeds in a nonstereospecific manner. Whereas the precursor substance exists as one stereoisomer, compound (**26**) is a mixture of two stereoisomers in a ratio of 30:70 (78DOK331). Stereoisomeric oxides and sulfides of (**27**) have been prepared.



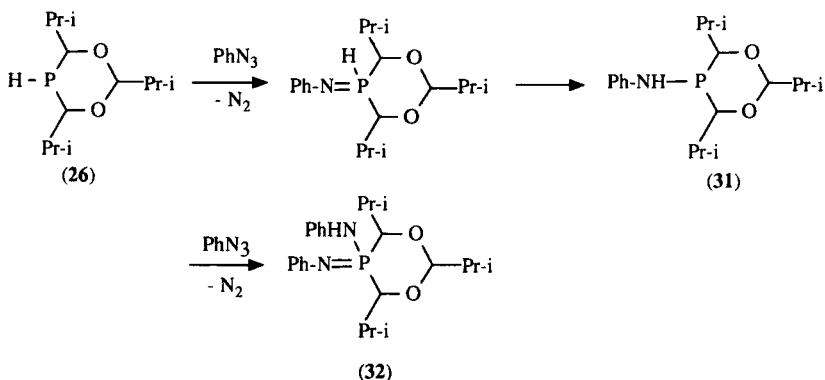
2,4,6-Triisopropyl-1,3,5-dioxaphosphorinane (**26**) and its sulfide react with chloral, *p*-fluorobenzaldehyde, and acetaldehyde [Eq. (18)]. In the latter case, the hydroxymethyl derivative (**29**) (R = Me) was obtained. The reaction with chloral and *p*-fluorobenzaldehyde does not stop at the addition stage, but proceeds further to form the oxides (**30**) (R = CCl₃, *p*-F-C₆H₄) (81IZV2776).



1,3,5-Dioxaphosphorinanes with substituents at ring carbon atoms have been obtained as a mixture of stereoisomers [78IZV1911; 79DOK(244)610, 79DOK(246)326, 79IZV866, 79IZV2136, 79IZV2239; 80IZV1626, 80IZV1630; 81IZV2803; 82IZV127]. The mixtures have been separated into individual stereoisomers by fractional crystallization, distillation, and chromatography. Equilibrium is reached more rapidly with sulfides than oxides. 1,3,5-Dioxaphosphorinanes with P(III) isomerize through the intermediate formation of protonated forms.

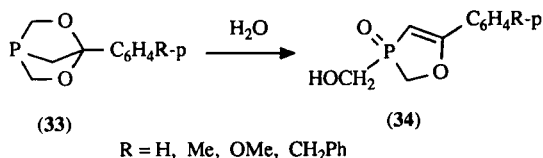
In the reaction of 1,3,5-dioxaphosphorinane (**26**) with phenyl azide, 5-phenylamino-5-phenylimino-2,4,6-triisopropyl-1,3,5-dioxaphosphori-

nananes (**32**) are formed, depending on the ratio of reagents [Eq. (19)] (83IZV2550).

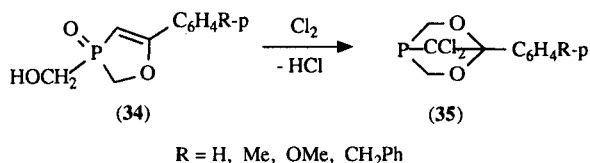


The initially obtained product undergoes isomerization and then the addition of phenyl azide to the phosphorus atom takes place. It is proposed that the oxidative imination does not depend on the steric effects of substituents. Actually, the interaction of 5-phenyl-2,4,6-triisopropyl-1,3,5-dioxaphosphorinane, existing as a mixture of three stereoisomers, gives with phenyl azide a mixture of three stereoisomers of 5-phenyl-5-phenylimino-2,4,6-triisopropyl-1,3,5-dioxaphosphorinane (83IZV2550).

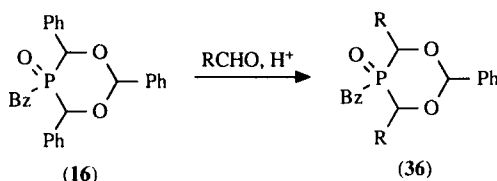
Reported also are transformations of bicyclic compounds with the P—C—O fragment. Thus, the oxidation of (**33**) by mercuric oxide is shown in Eq. (20) (70ZOB1673).



1-Phospha-3,5-dioxa-4-aryl-bicyclo[2.2.2]heptanes undergo similar transformation on heating with sulfur in benzene, resulting in the formation of 1-hydroxymethyl-1-thio-4-aryl-1-phospha-3-oxacyclopentenes-4 (72ZOB519). The inverse process is observed on chlorination of monocyclic oxides (**34**), which transform into bicyclic compounds (**35**) [Eq. (21)] (72ZOB519).



Phenyl groups at the 4,6-positions of the 1,3,5-dioxaphosphorinane ring may be replaced by others [Eq. (22)] (86M11). This reaction proceeds via the rupture of the ring in the presence of an acidic catalyst.



C. STEREOISOMERISM

Heterocycles with the P—C—X fragment, where X is a heteroatom, are of interest regarding the interaction between phosphorus and the heteroatom and its influence on conformational behavior. This interaction is most frequently considered a repulsion between lone electron pairs on phosphorus and the heteroatom, resulting in changes of substituent orientation, conformation of the ring, and inversion barriers. However, such an interpretation cannot explain all the existing data. Therefore a new concept was introduced: a donor–acceptor $n\text{--}\sigma^*$ interaction of the heteroatom's lone electron pair with the vacant orbital of the C—X bond (77M11). This interaction is maximal when the lone pair is *trans* to the C—X bond and results in anomalous orientation of substituents in the ring. Heterocycles containing the P—C—X fragment are convenient models for checking theories of conformational analysis. The field of conformational analysis of phosphorus-containing heterocycles has many possibilities due to high inversion barriers of the phosphorus atom, stereospecific values of spin–spin coupling constants $^2J_{\text{PH}}$, phosphorus chemical shifts, and large dipole moments of P=X bonds.

1. 1,3,5-Dioxaphosphorinanes

Several individual stereoisomers of substituted 1,3,5-dioxaphosphorinanes have been isolated [Eq. (23)] [79DOK(244)610, 79IZV2136; 80IZV1626; 83M11] (Table I). Their structure was established by the dipole moment method and further proved by determining dihedral angles with Albrand graphics (69BSF40) in the case of P(III) derivatives. The structure of P(IV) derivatives was proved by comparison with parent P(III) compounds.

Stereoisomers adopt a chair conformation with equatorial substituents at carbon (forms A and B, respectively), dioxaphosphorinane oxide, and

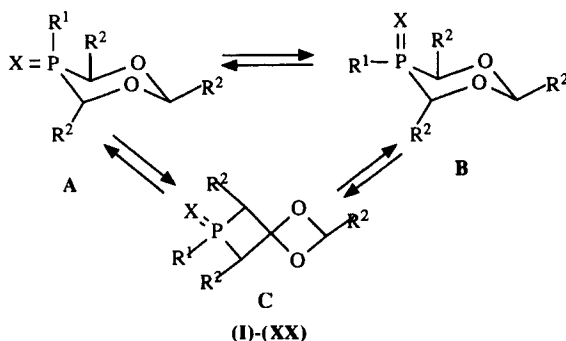


TABLE I
COMPOUNDS (I)-(XX)

	R ¹	R ²	X
I	Ph	H	Lone pair
II	Ph	H	O
III	Ph	H	S
IV	Ph	Me	Lone pair
V	Ph	Me	O
VI	Ph	Me	S
VII	Ph	Pr- <i>i</i>	Lone pair
VIII	Ph	Pr- <i>i</i>	O
IX	Ph	Pr- <i>i</i>	S
X	Ph	Ph	Lone pair
XI	Ph	Ph	O
XII	Ph	Ph	S
XIII	Me	Pr- <i>i</i>	Lone pair
XIV	Me	Pr- <i>i</i>	O
XV	Me	Pr- <i>i</i>	S
XVI	H	Pr- <i>i</i>	Lone pair
XVII	H	Pr- <i>i</i>	S
XVIII	OH	Me	O
XIX	OMe	Me	O
XX	CH ₂ Ph	Ph	O

sulfide with R = *i*-Pr being an exception. Their experimental dipole moments do not coincide with the values calculated for a chair conformation and may be explained by a conformational mixture with a prevailing twist form (form C). ¹H NMR spectra of these stereoisomers contain signals of nonequivalent protons attached to carbon atoms next to phosphorus, evidence in favor of twist conformations. Analysis of the values of spin-spin coupling constants ²J_{PH} and the structure of stereoisomeric model compounds leads to the conclusion that the coupling constants

depend on the stereochemistry. An inverse dependence of spin-spin coupling constants on the H—C—P—R dihedral angle was observed for both P(III) and P(IV) derivatives. The data on the equilibrium composition of stereoisomers for 1,3,5-dioxaphosphorinanes and their derivatives are summarized in Table II.

Of special interest (see Table II) is the structure of compound **XVI**, obtained in a reaction with thermodynamic control, and its sulfide (**XVII**), as both molecules contain the P—H bond. Infrared, Raman, and NMR studies as well as dipole moment measurements showed that the P—H bond was axial in these compounds. In some cases the conclusions of NMR and dipole moment studies were verified by X-ray single-crystal analysis.

Structural investigations of individual stereoisomers and equilibrium mixtures revealed some general features (83MI1). A phenyl group at phosphorus is predominantly in an axial position when there is no steric hindrance. The introduction of bulky substituents onto carbon atoms of the ring shifts the equilibrium toward an equatorial form, and one more twist conformer appears. The influence of equatorial substituents on the equilibrium position is clearly pronounced in the case of P(III) derivatives as well as for a P(IV) compound. The substitution of a phenyl group by a

TABLE II
EQUILIBRIUM CONFORMATIONAL COMPOSITION
OF 1,3,5-DIOXAPHOSPHORINANES AND THEIR
DERIVATIVES (%)

	Conformer		
	A	B	C
I	72	28	0
II	100	0	0
III	100	0	0
IV	86	14	0
V	79	21	0
VI	92	8	0
VII	22	64	14
VIII	54	46	0
IX	0	52	48
X	0	100	0
XI	0	100	0
XII	0	100	0
XIII	30	70	0
XVI	100	0	0
XX	0	21	79

methyl substituent at phosphorus does not lead to any significant changes in equilibrium position. On the contrary, the benzyl group sharply increases the amount of twist conformer in the mixture. The phosphorus atom coordination does not influence the equilibrium position when substituents at the neighboring carbon atoms are small.

A comparison of 1,3,5-dioxaphosphorinanes with the corresponding 1-phenylphosphorinanes shows that substitution of the methylene group by oxygen results in a shift of the equilibrium toward the conformer with an axial orientation of substituent at phosphorus.

2. Miscellaneous Heterocycles

Since the influence of an oxygen atom on phosphorus should depend on its environment, we studied dioxaphosphorinane analogues, such as 1,3,2,5-dioxasilaphosphorinanes (7) and 1,3,2,5-dioxaboraphosphorinanes. The latter will be thoroughly discussed in Section IV. 1,3,2,5-Dioxasilaphosphorinane (7) has been described [79DOK(247)609] (Fig. 1).

Comparison of calculated and experimental values of dipole moments reveals the possibility of a conformational equilibrium between two chair-like conformations, the phosphorus lone electron pair being equatorial in the major conformer according to NMR data. The prevailing conformer (85%) of 1,3,2,5-dioxasilaphosphorinane sulfide **37** has an axial phenyl group at phosphorus (Fig. 1).

NMR data of 1,3,5-azoxaphosphorinanes (8) are analyzed in several references [73ZC(13)291; 74MI1]. The comparison of spin-spin coupling constants for 1,3,5-azoxaphosphorinanes with those for 1,3,5-dioxaphosphorinanes made it possible to establish the conformation of substituents in 1,3,5-azoxaphosphorinanes (83MI1). All four stereoisomers adopt a chair conformation with equatorial phenyl groups, including that at phosphorus.

The aspects of synthesis, chemical properties, and conformational behavior considered above are very useful for a discussion of the properties of compounds containing P—C—N and P—C—O—B fragments. They may be also applied in the more complicated field of coordination compounds of cyclic functionally substituted phosphines.

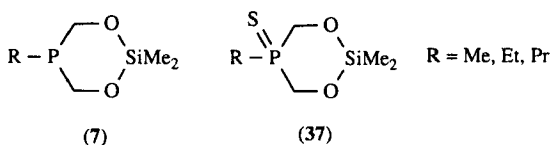


FIG. 1.

III. Heterocycles with P—C—N Fragments

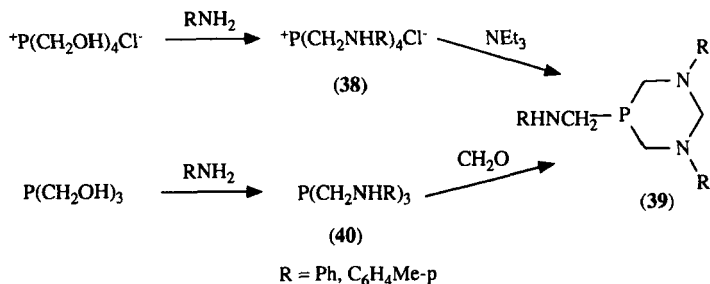
Compounds with the P—C—N fragment are well known and widely studied due to their stability and simple methods of synthesis. There is a series of reviews considering aminomethyl derivatives of phosphines including cyclic structures (74UK2044; 81MI1; 84UK625; 84ZC365; 86MI1). A survey concerning methods of synthesis of various compounds, containing a P—C—N fragment, by the Mannich reaction can be found (84ZC365). Therefore, here we discuss only the basic data on heterocyclic compounds with the P—C—N fragment

A. SYNTHESIS

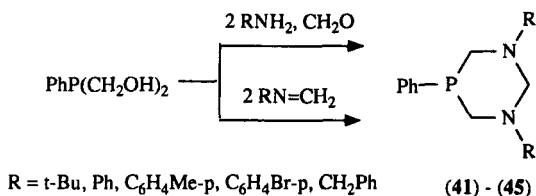
Most of the compounds with the P—C—N fragment are the aminomethyl derivatives of phosphines, as the synthesis of the α -aminoalkyl derivatives of phosphines is more complicated. α -Hydroxyalkyl derivatives of phosphines dissociate to give phosphine and aldehyde or ketone, thereby causing subsequently an undesirable condensation of amines with aldehydes and ketones in the reaction with α -hydroxyalkylphosphines. And hydroxymethyl derivatives are much less likely to dissociate. There are two possible mechanisms for the formation of the α -aminomethyl fragment from the α -hydroxyalkyl group. The first proceeds via the dissociation of α -hydroxyalkylphosphine with formation of phosphine and the carbonyl compound, followed by interaction of the latter with amine by the addition of phosphine to the C=N bond. The second mechanism employs a nucleophilic substitution at the α -carbon atom of a hydroxyalkylphosphine by the action of amine. The second is more useful because the reaction proceeds even in the absence of a labile hydrogen atom in the interacting molecules, when the possibility of the dissociation is excluded. For example, the interaction of 1,3,5-dioxaboraphosphorinane with 1,3,5-diazaphosphorinane gives 1,5,3,7-diazadiphosphacyclooctanes (see Section IV). However, one cannot exclude the presence of catalytic amounts of water and alcohol in this case as well.

1. 1,3,5-Diazaphosphorinanes

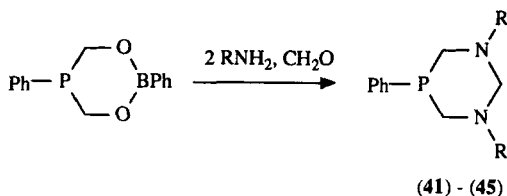
The main method for obtaining these heterocycles is the interaction of amines with oxymethylphosphines. Frank and Drake (72JOC2752; 77JOC4040) isolated 5-aminomethyl-1,3-diphenyl-1,3,5-diazaphosphorinane (**39**) by treating tris(oxymethyl) phosphine (**40**) or tetrakis(oxymethyl)phosphonium chloride (**38**) with aniline. The reaction with *p*-toluidine proceeds in a similar manner [Eq. (24)] (83IZV1379).



A series of 1,3,5-diazaphosphorinanes (**41**–**45**) was obtained from phenyl(hydroxymethyl)phosphine (79IZV2771; 80IZV721, 80IZV735, 80IZV952, 80IZV1571, 80IZV2129, 80MI1; (81DOK127, 81IZV1539, 81IZV2279; 82DOK650; 83IZV1846, 83MI1; 84MI1; 86MI1; 89IZV1340). Reactions with aromatic amines and benzylamine proceed exothermically in the presence of paraformaldehyde with and without solvent. The aforementioned reactions with aliphatic primary amines result in the formation of oligomers. Azomethines may be used instead of amines [Eq. (25)].



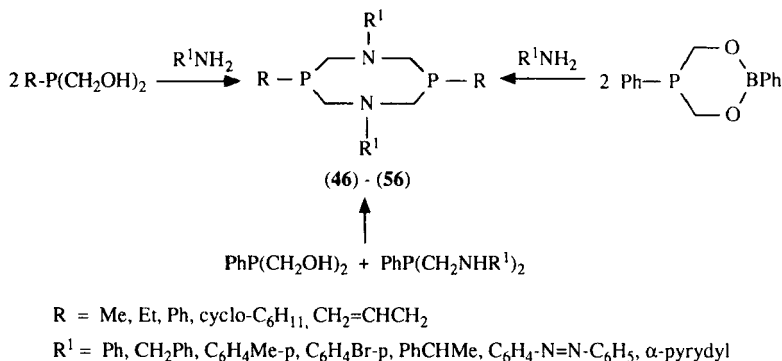
1,3,5-Diazaphosphorinanes (**41**)–(**45**) may be obtained by interaction of compounds containing the P—C—O—B fragments with amines [Eq. (26)]. They will be discussed in Section IV.



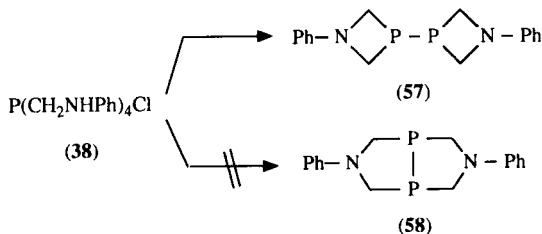
2. 1,5,3,7-Diazadiphosphacyclooctanes

Depending on the relative amount of reagents, three types of products may be obtained in the reaction of hydroxymethylphosphines with amines: acyclic aminomethylphosphines, 1,3,5-diazaphosphorinanes, and 1,5,3,7-diazadiphosphacyclooctanes. Indeed, the interaction of phosphorus-containing diols with 1 mol of amine gives eight-membered heterocycles. The initial assumption about the formation of 1,3-azaphosphetidines

(80IZV735) was incorrect. An X-ray structural investigation (80IZV2129; 81DOK127, 81IZV2279; 82DOK650) showed that the products are 1,5,3,7-diazadiphosphacyclooctanes **(46)**–**(56)**—dimers of azaphosphetidine. The reactions proceed exothermically with a quantitative yield of the final products. It should be noted that all attempts to isolate the intermediate compounds with one hydroxy group and also those substituted by an amino group failed. A large series of 1,5,3,7-diazadiphosphacyclooctanes **(46)**–**(56)** was described by Markl [Eq. (27)] (80TL1409).



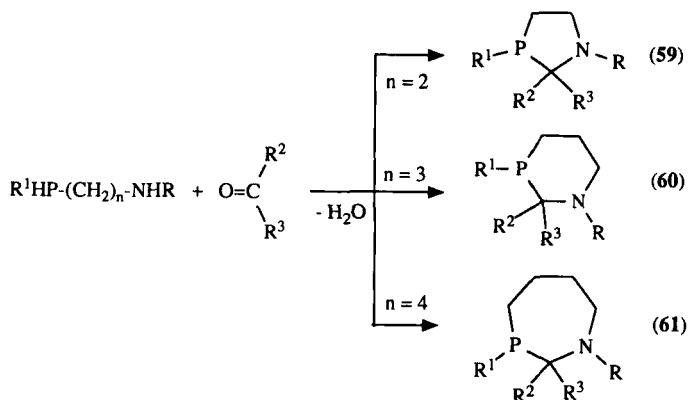
However, compound **57**, containing two 1,3-azaphosphetidine fragments, obtained by heating tetrakis(aminomethyl)phosphonium **(38)** chloride or tris(anilinomethyl)phosphine **(40)** in ethanol, is described in Eq. (28) (72JOC2752; 77JOC4040). A detailed analysis of NMR spectra made it possible to reject a structure with two five-membered rings.



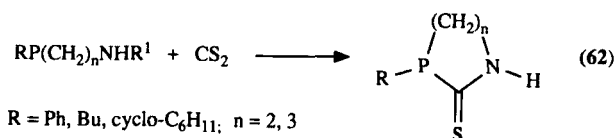
3. Miscellaneous Heterocycles

Condensation of ketones with aminoalkylphosphines, containing hydrogen atoms at phosphorus and nitrogen, results in the formation of 1,3-azaphospholanes **(59)** (67CB2685; 68CB3619, 1,3-azaphosphorinanes **(60)** (68CB4032; 73JPR526), and 1,3-azaphosphhepanes **(61)** [Eq. (29)] [73ZC(19)139].

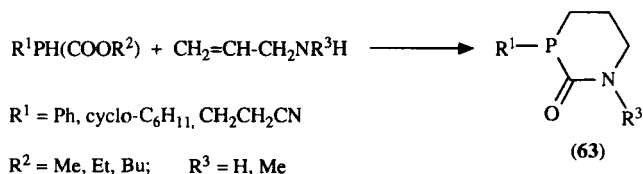
The reaction with phosphines, which have a primary amino group as a substituent, proceeds in a similar manner. Interaction with carbon



disulfide results in the formation of 1,3-azaphospholanes and 1,3-azaphosphorinanes with a thioketone group in the ring [Eq. (30)] (78JPR600).



1,3-Azaphosphorinanes (**63**) with a ketone group in a ring were obtained (82ZN965) by the intramolecular cyclization of aminopropyl(alkoxycarbonyl)phosphines in the presence of azobisisobutyronitrile [Eq. (31)].

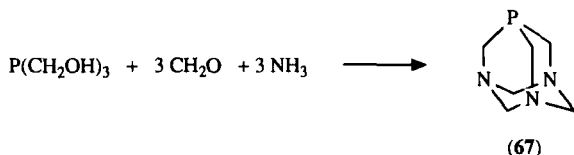
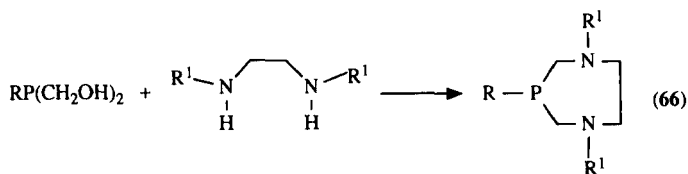


Synthesis of a great variety of heterocyclic structures becomes possible on utilization of hydrazines. Diazaphospholanes (**64**) and (**65**) were obtained by the interaction of bis(hydroxymethyl)phosphine with hydrazines [Eq. (32)] (81TL229).



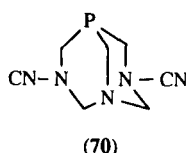
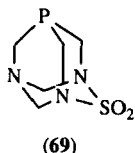
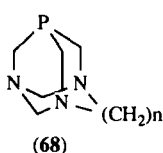
The introduction of ethylenediamines into this reaction resulted in the formation of seven-membered heterocycles (**66**) [Eq. (33)] (81TL3467).

Heterocycles, belonging to the series of 3,5,7-triaza-7-phosphaadamantane (**67**), which are of theoretical interest and importance, are described in several references (74MI2; 75CZ246) [Eq. (34)]. These rigid bicyclic

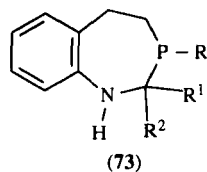
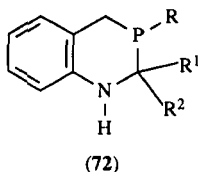
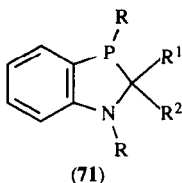


molecules adopt chair conformations, each containing three heteroatoms with all the lone electron pairs being in equatorial positions. These bicyclic compounds can serve as models for studying the spatial structure of six-membered heterocycles.

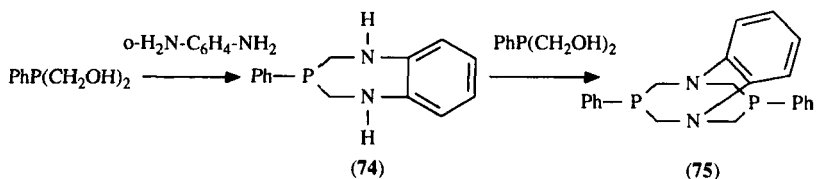
Some homologues and analogues of triazaphosphaadamantane (68)–(70) have been described [Eq. (35)] (74MI3; 75MI1; 81VSP374584; 82PS105).



A series of heterocyclic compounds, containing the P—C—N and *o*-substituted aminophenylene fragment have been synthesized [Eq. (36)]. These are benzazaphospholenes (71), benzazaphosphorinanes (72), and benzazaphosphepanes (73) (70-71MI1; 74MI1; 76MI1).



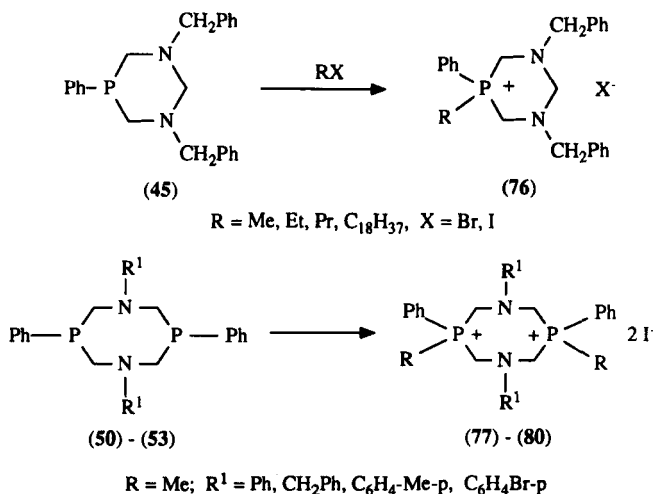
Heterocycles (74) and (75), obtained by the interaction of bis(oxy-methyl)phenylphosphine and *o*-phenylenediamine [Eq. (37)], have been described (82IZV440).



B. REACTIONS

The reactivity of cyclic aminomethylphosphines is of special interest due to the presence of two or more heteroatoms capable of quarternization in a 1,3-position. Besides the ordinary oxidation of tricoordinated phosphorus, mutual transformations and rearrangements are typical.

Alkylation of 1,3,5-diazaphosphorinanes (**45**) proceeds exclusively at the phosphorus atom unlike acyclic compounds (83IZV1379) [Eq. (38)]. Similar reactions were observed for 1,5,3,7-diazadiphosphacyclooctanes (**50**)–(**53**) [Eq. (39)]. Only the phosphorus atom was alkylated even in excess alkyl halide.

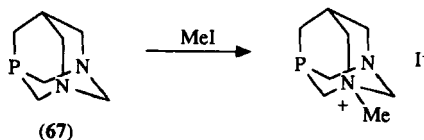


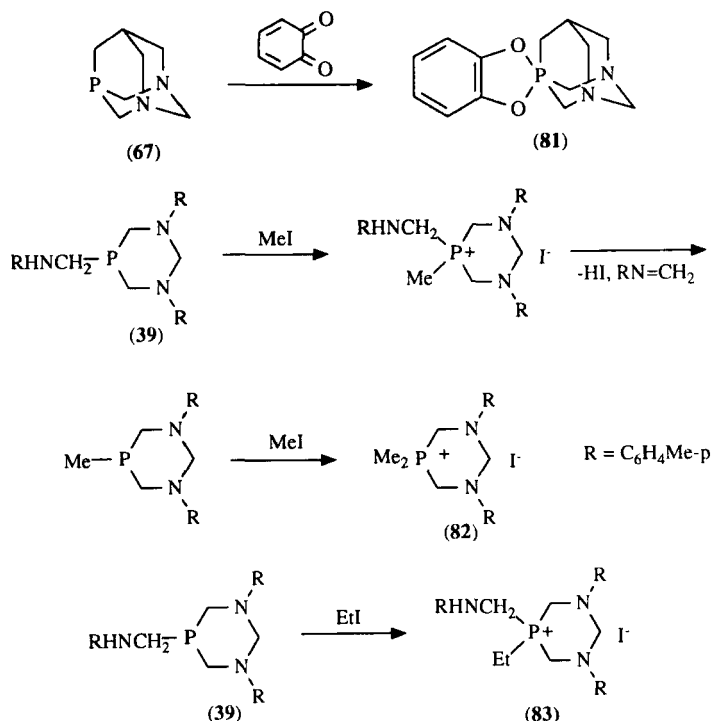
At the same time it was shown (74MI2) that 1,3,5-triaza-7-phosphaadamantane (**67**) adds methyl iodide at one of its nitrogen atoms [Eq. (40)].

Phosphaadamantane (**67**) reacts with *o*-quinones to give phosphoranes (**81**) [Eq. (41)] (83PS51).

An interaction of 1,3,5-diazaphosphorinane (**39**) with methyl iodide results in the formation of 5,5-dimethyl-1,3,5-diazaphosphorinane iodide (**82**) [Eq. (42)] (83IZV1379).

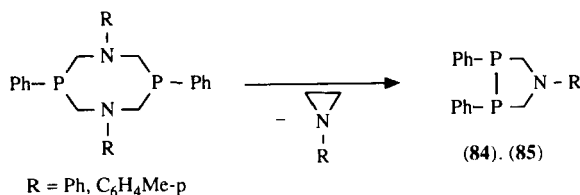
Alkylation primarily at the phosphorus atom with the formation of a chiral phosphonium salt was proved by an investigation of the interaction





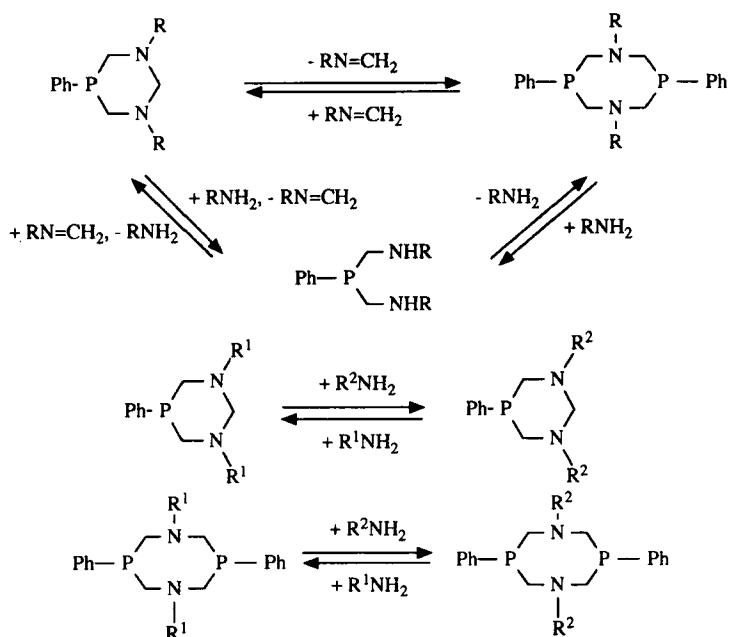
between (39) and ethyl iodide [Eq. (43)]. The stability of the alkylation products seems to depend on the type of alkyl substituents.

1,5,3,7-Diazadiphosphacyclooctanes transform into five-membered rings—1,3,4-azadiphosphacyclopentanes (84), (85)—on heating above the melting point [Eq. (44)] (82IZV1436).



Amino groups of functionally substituted phosphines easily undergo nucleophilic substitution. Mutual transitions were shown to exist for the aminomethyl derivatives of phenylphosphine (80IZV1438), acyclic compounds being transformed into cyclic ones with variation in the size of the rings [Eq. (45)].

Substitution of one amino group by another without any skeletal changes has been studied [Eq. (46)] (80IZV2417). These transitions are reversible



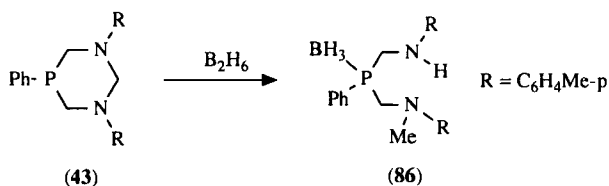
and the reaction direction is determined by the conditions and by the solubility of compounds.

Formation, transamination, and mutual transitions of aminomethyl derivatives of phosphines, representing nucleophilic substitution at the carbon atom in the P—C—O(N) fragment, take place under milder conditions than similar reactions of alcohols and amines. The reason is likely the participation of a phosphino group in intramolecular interactions (86MI1).

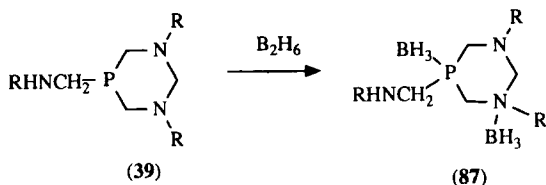
Aminomethylphosphines are convenient objects for a comparison of phosphorus and nitrogen donor ability in complexation reactions. Coordination compounds of heterocyclic aminomethylphosphines with metals are discussed in Section VII. In this section we present reactions of aminomethylphosphines with boranes (BH₃).

A number of studies [74JCS(D)1510; 76MI2] have shown that each molecule of tris(aminomethyl)phosphine is coordinated by three or four molecules of BH₃. In view of this, one can conclude that coordination proceeds not only at phosphorus but also at nitrogen atoms.

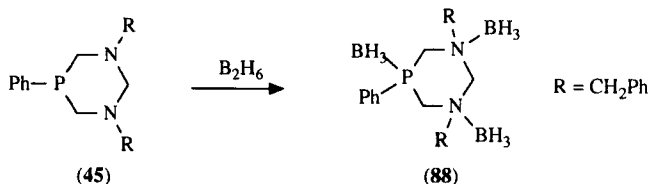
The interaction of cyclic aminomethylphosphines may proceed either with opening of the ring or with its preservation (89IZV1375). 1,3,5-Diazaphosphorinane (**43**) with R = C₆H₄Me-*p* at the nitrogen atoms, when treated by diborane, opens its ring with rupture of the C—N bond in the N—C—N fragment and coordination of the borane molecule at the phosphorus atom [Eq. (47)].



Compound (39) reacts under the same conditions with retention of the ring, giving the complex with two borane molecules (87) [Eq. (48)].

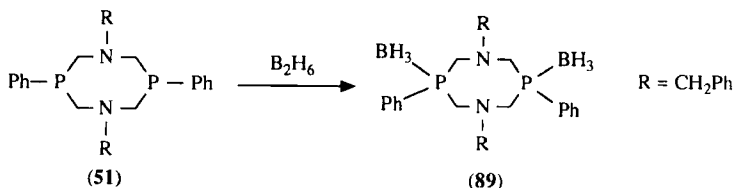


1,3,5-Diazaphosphorinane (45), containing benzyl groups at the nitrogen atoms, forms complex (88) with three borane molecules [Eq. (49)].



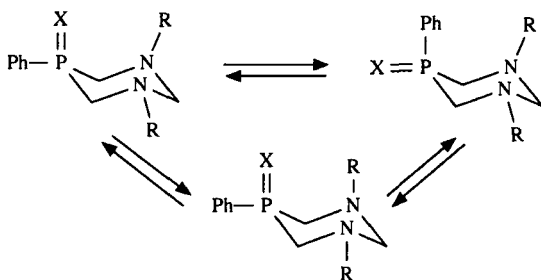
Structural studies of the initial diazaphosphorinanes and their complexes revealed a close connection between the structure of the former and the number of coordinating borane molecules. When substituents of a diazaphosphorinane with $\text{R} = \text{Ph}$ are equatorial, addition of three molecules of borane in the axial position is not energetically favorable. In the case of $\text{R} = \text{CH}_2\text{Ph}$ there is a form with one axial substituent; hence the third molecule of borane may approach the equatorial nitrogen lone electron pair (89IZV1375).

1,5,3,7-Diazadiphosphacyclooctane (51) interacts with only two molecules of borane with participation of the phosphorus atoms [Eq. (50)]. The number of borane molecules added is likely to be determined by the conformation of the eight-membered ring, which exists in a distorted boat-boat form similar to that of the analogous sulfide.



C. CONFORMATIONAL FEATURES

1. 1,3,5-Diazaphosphorinanes



X = lone pair, O, S, Se; R = Ph, C₆H₄Me-*p*, C₆H₄Br-*p*, CH₂Ph

1,3,5-Diazaphosphorinanes exist as a mixture of three conformers in solution [Eq. (51)], although all heteroatoms in the ring have substituents. Conformational equilibrium is due to the low inversion barrier of nitrogen studied by ¹H NMR and the dipole moment method (83MI1; 84MI1) [Eq. (51)]. The results are presented in Table III.

For R = Ar there are two forms participating in the equilibrium; they are characterized by the orientation of the substituent at phosphorus. For 1,3,5-diazaphosphorinane there is 24–36% of the conformer with the axial

TABLE III
PERCENTAGE OF CONFORMER WITH AN AXIAL
PHENYL GROUP AT PHOSPHORUS IN 1,3,5-
DIOXAPHOSPHORINANES

X	R	%
Lone pair	Ph	24
	C ₆ H ₄ Me- <i>p</i>	33
	C ₆ H ₄ Br- <i>p</i>	0
	CH ₂ Ph	36
O	Ph	56
	C ₆ H ₄ Me- <i>p</i>	54
	C ₆ H ₄ Br- <i>p</i>	50
	CH ₂ Ph	78
S	Ph	70
	C ₆ H ₄ Me- <i>p</i>	70
	C ₆ H ₄ Br- <i>p</i>	70
	CH ₂ Ph	72
Se	Ph	68
	C ₆ H ₄ Me- <i>p</i>	57
	C ₆ H ₄ Br- <i>p</i>	78
	CH ₂ Ph	54

phenyl group at phosphorus. The amount of this conformer increases in the series, being 50–56% for oxides, 70% for sulfides, and 57–78% for selenides. The benzyl group at nitrogen stabilizes a conformation with the axial substituent at one of the nitrogen atoms.

Unlike 1,3,5-dioxaphosphorinanes the relative population of the conformer with the axial phenyl group at phosphorus decreases in 1,3,5-diazaphosphorinanes both for P(III) and for P(IV) compounds. Conformational analysis of 5-phenyl-1,3,5-diazaphosphorinanes and their oxides, sulfides, and selenides showed that the conformational equilibrium shifted toward the conformer with the axial phenyl group on changing from P(III) to P(IV) derivatives. The same conclusion made for 5-phenyl-1,3,5-dioxaphosphorinanes, but it is contrary to that made for 1-phenylphosphorinane-4-ones and their derivatives (83MI1).

2. Miscellaneous Heterocycles

An NMR study (74MI4) of a series of 1,3,5-azaioxaphosphorinanes (**8**) revealed highly stereospecific H^1-H^1 coupling constants in the 4,6-positions of the heterocycle. The conformation of the ring and an orientation of substituents were established for 1,3,5-dioxaphosphorinanes (**1–4**) and 1,3,5-azaioxaphosphorinanes (**8**) by a comparison of their coupling constants (83MI1). All four stereoisomers adopt a chair conformation with equatorial phenyls, including the phenyl group at phosphorus.

The spatial structure of 16 stereoisomers of 1,3-aza-, 1,3-thia-, and 1,3-oxaphospholanes was determined (75OMR470). 1H NMR spectra of several stereoisomers of phospholanes, containing N and O atoms in the 3-position to phosphorus, have been presented [78PS(4)59; 83PS51]. However, the conformational equilibrium was not studied (Fig. 2).

Chemical properties and structure of heterocycles containing P—C—O and P—C—N fragments are determined by the interaction between the heteroatoms. This interaction is most clearly pronounced in heterocyclic compounds also possessing an acceptor functional group (B(III), O—B(III), N—B(III), etc.).

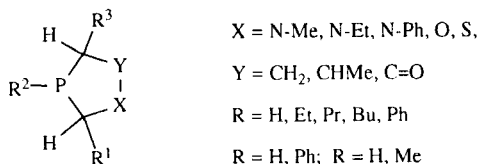


FIG. 2.

IV. Heterocyclic Compounds with P—C—O—B Fragments

Over the past 10 years the chemistry of P,B-containing compounds, obtained from α -hydroxyalkylphosphines, has been extensively studied. Unusual and diverse properties of P,B-containing compounds, mostly cyclic, are due to a fortunate combination of heteroatoms. A series of studies extended the scope of the investigations to other classes of heterocyclic compounds containing phosphorus and boron atoms. The present survey covers only those P,B-containing heterocycles that are derivatives of functionally substituted phosphines. Phosphine-boranes (—P—B—)_n and phosphino-boranes ($\text{—P}\rightarrow\text{B—}$) have been reported in several reviews (67MI1; 82MI1, 82MI2).

The presence of two heteroatoms with different electronic properties in one molecule (one atom possessing a lone electron pair and another one with a vacant orbital, donor and acceptor, base and acid) separated by some fragment results in an interaction between the heteroatoms. Three types of the phosphorus–boron interactions have been revealed: through-bond, intramolecular trans-annular (dative P—B bond), and intermolecular (dative P—B bond) (Fig. 3).

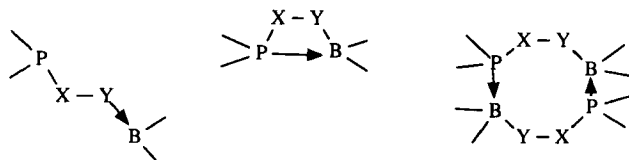


FIG. 3.

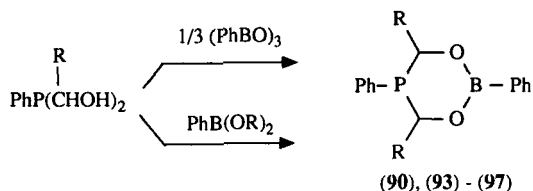
The type of interaction and its chemical influence are determined by phosphorus and boron coordination, by the type of the fragment separating them, and by molecular structure. Thus, it is reasonable to classify P,B-containing heterocycles according to the type of fragment separating phosphorus and boron.

All the compounds summarized in this review can be divided into the following groups: heterocycles with P—C—B, P—C—O—B, P—C=C—B, P—C=C—O—B, P—C—N—B, P—(C)_n—B fragments, and a special group of coordination compounds.

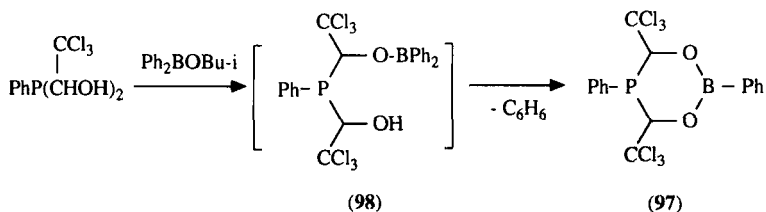
A. SYNTHESIS

The main synthetic method for obtaining boroxyalkyl phosphorus derivatives, i.e., compounds with the P—C—O—B fragment, is the transesterification of α -hydroxyalkylphosphines with boric acid esters or esteri-

Bis(α -hydroxyalkyl)phosphines are readily converted into cyclic compounds by derivatives of boric acids. In the case of the diethyl ester and anhydride of diphenylboric acid, 1,3,2,5-dioxaboraphosphorinanes (**90**), (**93**)–(**97**) were obtained [Eq. (55)] (79IZV2349; 80IZV1438; 83IZV1374, 83IZV2535, 83IZV2545; 84IZV2501; 85IZV1102). The presence of strong acceptor substituents in a α -hydroxyalkylphosphine causes transformations of the primary trans-esterification product (**98**) [Eq. (56)] (85IZV1102). 1,3,2,5-Dioxaboraphosphorinanes with donor and acceptor substituents in the 4,6-positions of the heterocycle were obtained, providing an opportunity to study the role of the interaction between the heteroatoms in the P—C—O—B fragment.



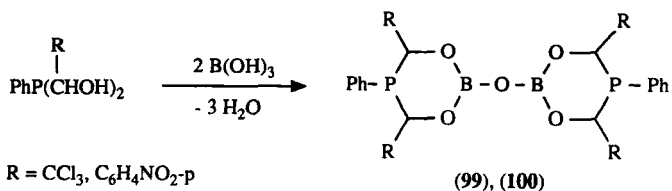
R = H (**90**), Me (**93**), Pr-i (**94**), Ph (**95**), C₆H₄NO₂-p (**96**), CCl₃ (**97**)

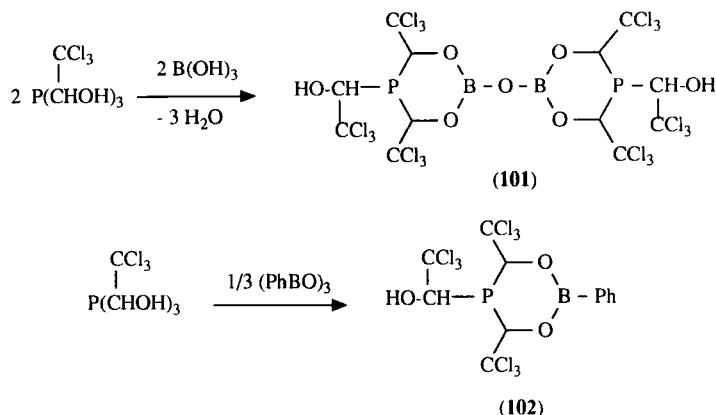


In the case of boric acid, the products with two 1,3,2,5-dioxaboraphosphorinane rings (**97**), (**98**) are obtained as water was removed azeotropically [Eq. (57)] (85IZV1102).

Similar bicyclic **101** was obtained from tris(α -hydroxy- β,β,β -trichloroethyl)phosphines and boric acid [Eq. (58)].

Interaction between tris(α -hydroxy- β,β,β -trichloroethyl)phosphines and the anhydride of phenylboric acid gave rise to 1,3,2,5-dioxaphosphorinanes (**102**) with 5- α -hydroxy- β,β,β -trichloroethyl substituents [Eq. (59)].

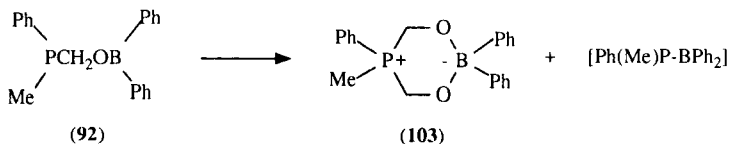




Heterocyclic compounds of the 1,3,2,5-dioxaboraphosphorinane series can be obtained from appropriate P,B-containing molecules.

2. 1,3,2,5-Dioxaborataphosponiarinanes

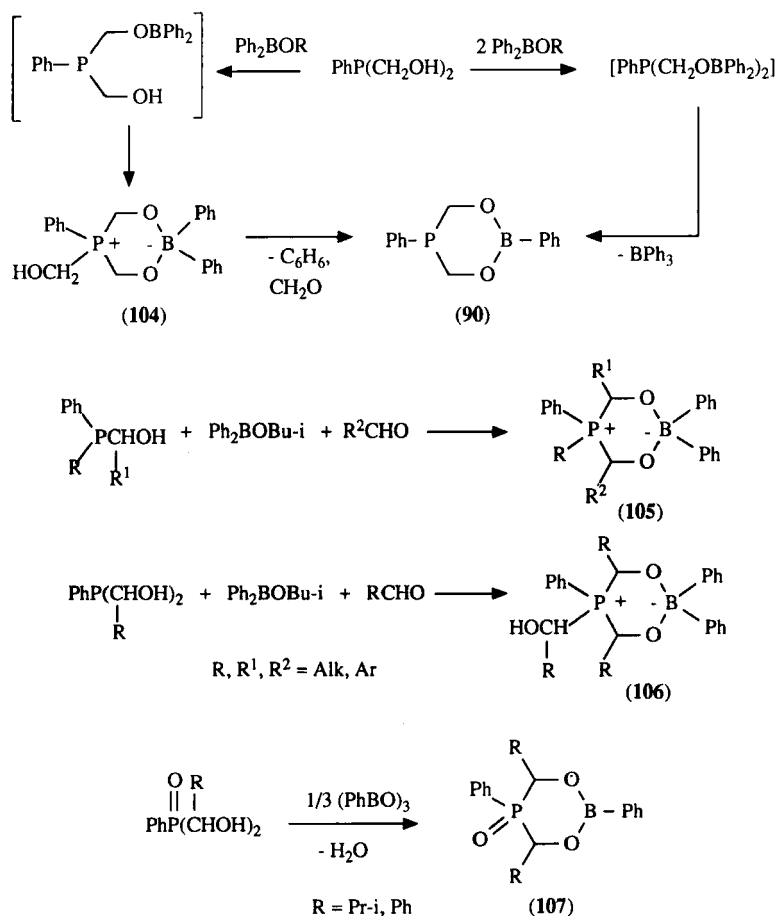
Acyclic boryloxyalkylphosphines with tricoordinated phosphorus and boron are capable of forming cyclic betaine structures with four-coordinated P and B atoms. The ability to be converted into a more stable four-coordinated state accounts for many chemical transformations of boryloxyalkylphosphines. Diphenylboryloxymethyl(methyl)phenylphosphine (**92**) readily disproportionates to give 1,3,2,5-dioxaborataphosponiarinane (**103**). [Eq. (60)] (83IZV2541). Similar interaction is



observed between bis(oxymethyl)phenylphosphine and diphenylboric acid ester [Eq. (61)] (79IZV2349; 80IZV1438; 81IZV1545; 84UK625; 86MI1; 90MI1).

Borylation in the presence of aldehydes makes it possible to obtain asymmetric dioxaborataphosponiarinanes (**105**), (**106**) [Eq. (62)] (83IZV2541; 85IZV2359; 86IZV2502).

In contrast to α -hydroxyalkylphosphine, the derivatives of α -hydroxyalkylphosphines (oxides, sulfides, selenides) are borylated only under severe conditions or do not react at all. Thus diphenylboric acid esters do not react with α -hydroxyalkylphosphine oxides even on prolonged heating. 2,5-Diphenyl-5-oxo-1,3,2,5-dioxaboraphosphorinanes (**107**) were obtained

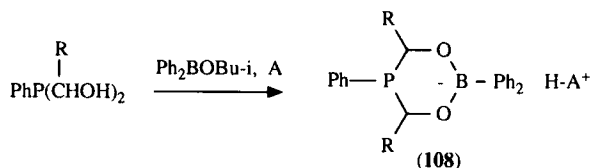


from oxides of diols and the anhydride of phenylboric acid as water was azeotropically removed [Eq. (63)] (83IZV1374).

3. Ammonium 1,3,2,5-Dioxaborataphosphorinanes

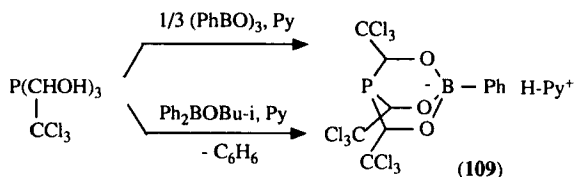
Compounds belonging to this series are of special interest because they exhibit the properties of both cyclic and acyclic structures as a result of ion complex tautomerism. They were obtained via borylation of hydroxy-alkylphosphines in the presence of tertiary amines [Eq. (64)], whereas primary and secondary amines give aminomethylphosphines under such conditions (84UK625; 86JZV1641, 86MI1; 90MI1).

The interaction of tris(α -hydroxy- β,β,β -trichloroethyl)phosphine with phenylboric acid anhydride in the presence of triethylamine yields resins.

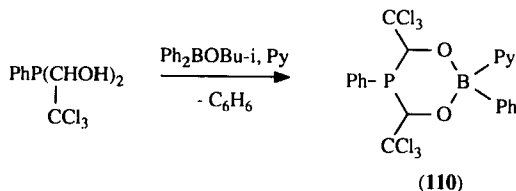


R = H, Alk, Ar; A = NEt₃, NBu₃, MeN(CH₂CH₂)₂O

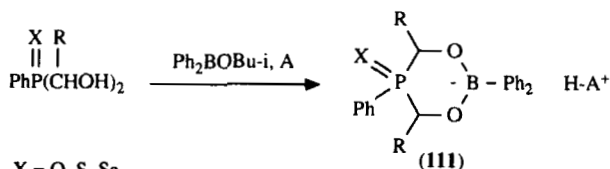
But in the presence of pyridine, 1-borata-2,6,7-trioxa-4-phosphabicyclo[2,2,2]octane (**109**) has been obtained [Eq. (65)]. The course of the reaction does not depend on the replacement of phenylboric acid anhydride by its ester (85IZV469; 86JZV1641).



The ability of α -hydroxyalkylphosphines with acceptor substituents to eliminate benzene on esterification with diphenylboric acid esters is so characteristic that it is impossible to obtain the intermediate esterification product even in the presence of pyridine. Instead of pyridinium dioxaborataphosphorinane, the complex (**110**) of dioxaboraphosphorinane with pyridine was isolated [Eq. (66)] (86IZV643).



As mentioned above, oxides, sulfides, and selenides of α -hydroxyalkylphosphines react with diphenylboric acid anhydride under severe conditions. The same is true for diphenylboric acid ester. For example, the reaction with bis(hydroxymethyl)phenylphosphine does not proceed even on prolong heating in solution. However, the presence of organic bases drastically changes the situation. Interaction takes place at room temperatures, sometimes exothermically, and gives the corresponding ammonium 1,3,2,5-dioxaborataphosphorinanes (**111**) [Eq. (67)] (84IZV2089, 84UK625; 85IZV2362, 85IZV2369; 86IZV171, 86MI1; 88IZV187; 90MI1). It should be noted that in the present case it is possible to use primary and secondary amines and also hydrazines (90MI2), as α -hydroxyalkylphosphine derivatives are inert to these amines under mild conditions.



X = O, S, Se

R = H, Alk, Ph, CCl₃, C₆H₄NO₂-p, C₆H₄Cl-p

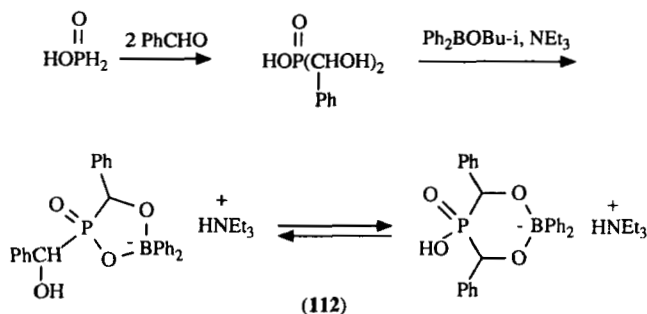
A = NEt₃, Py, EtN(CH₂CH₂)₂CH₂, Pr₂NH, BuNH₂, p-MeC₆H₄NH₂, HSCH₂CH₂NH₂,

HOCH₂CH₂NH₂, HO(CH₂)₂NH₂, t-C₈H₁₇NH₂, NH₃

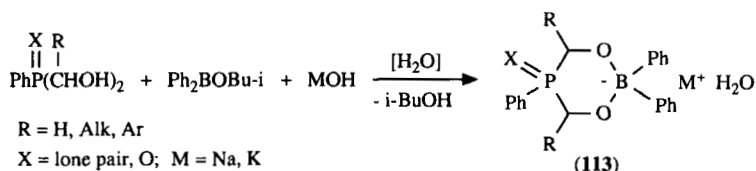
R¹R²NR³R⁴ R¹ = H, Me, Pr-i; R², R⁴ = H, Me; R³ = H, Ph

Although the borylation reaction of α -hydroxyalkylphosphine derivatives can be considered autocatalyzed, the catalyst is incorporated into the final reaction product.

The participation of a large number of amines in this reaction makes it possible to obtain functionally substituted nitrogen-containing bases. These compounds, as well as their tricoordinated phosphorus analogues, are capable of ion complex tautomerism, with new types resulting from the presence of functional groups in the ammonium cation. In addition to phosphines other classes of organophosphorus compounds undergo a borylation reaction with diphenylboric acid ester due to its activation by amines. For example, α -hydroxyalkyl derivatives obtained from hypophosphorous acid are also borylated in the presence of amines [Eq. (68)] (87ZOB2639).

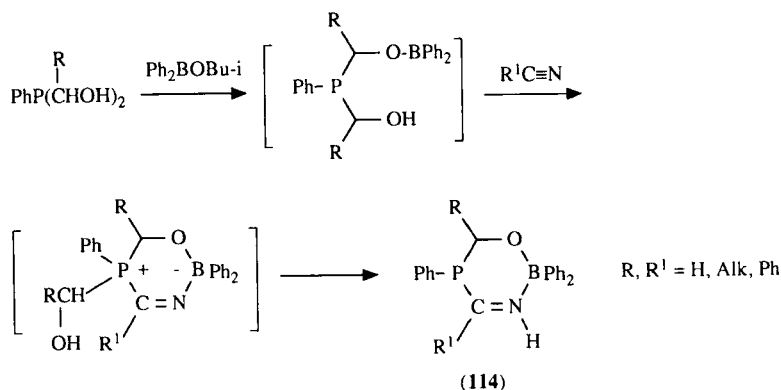


In addition to amines, alkali metal alkoxides, hydroxides, and metals themselves can be used in borylation reactions [Eq. (69)] (90IZV886).



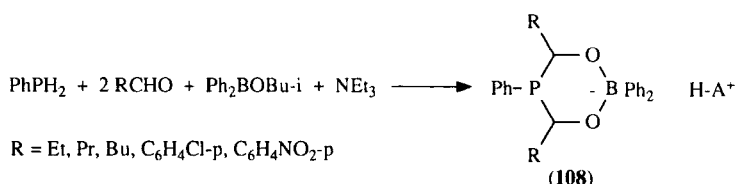
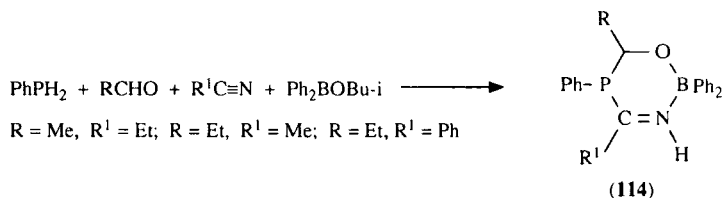
4. Boryloxyalkyl(imido)phosphines

Borylation in the presence of additional reagents are of paramount importance due to the possibility of obtaining new types of structures. For example, interaction of α -hydroxyalkylphosphines with diphenylboric acid ester in the presence of nitriles results in the formation of boryloxyalkyl(imido)phosphines (**114**) [Eq. (70)] (82IZV676).

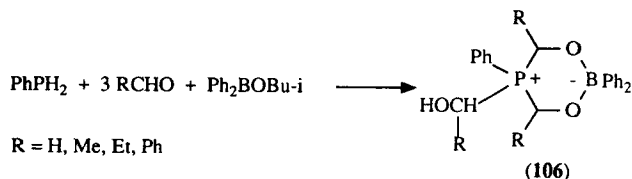


5. Miscellaneous Types and Methods

Identical conditions for the synthesis of α -hydroxyalkylphosphines and for borylation make it possible to combine the formation of α -hydroxyalkylphosphines and their interaction with boric acids derivatives. As a rule, in all the examples cited below, there is one single course of reaction without any by-products. Thus, diphenylboryloxyalkyl(imido)phosphines (**114**) [Eq. (71)], ammonium 1,3,2,5-dioxaborataphosphorinanes



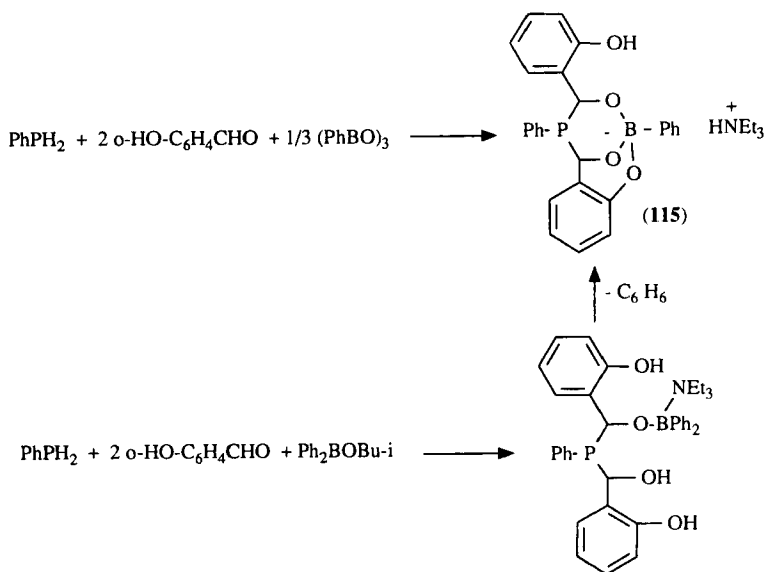
(108) [Eq. (72)], and 1,3,2,5-dioxaborataphosphoniarinanes **(106)** [Eq. (73)] were obtained from phenylphosphine without isolation of α -hydroxyalkylphosphines (85IZV2359; 86IZV2510; 87IZV2118; 88IZV159).



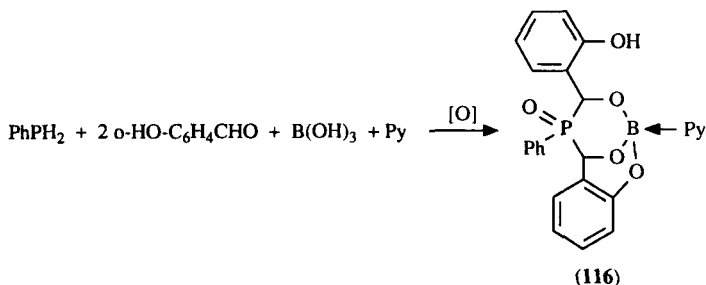
As a rule, the order of mixing reagents is of no importance. The addition of sulfur or selenium into the reaction mixture in a last stage makes it possible to obtain corresponding derivatives.

The possibility of carrying out a multistep synthesis makes it possible to obtain P,B-containing derivatives from unstable intermediate α -hydroxyalkylphosphines. Thus, phenylphosphine, salicylic aldehyde, phenylboric acid anhydride, and triethylamine interact to give a bicyclic product—2,8,9-trioxa-1-borata-4-phospha-6,7-benzobicyclo[3,3,3]nonane (**115**) [Eq. (74)] (87IZV2118; 89IZV946). In this case an aldehyde takes part in the reaction opening up new synthetic possibilities.

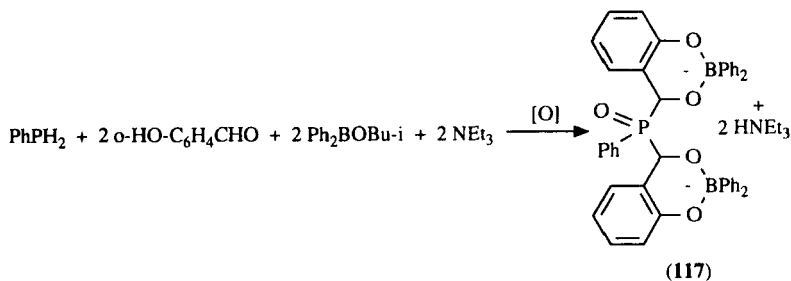
Analogous products have been obtained when salicylic aldehyde was replaced by *o*-hydroxynaphthaldehyde.



The reaction of phenylphosphine with boric acid and 2 mol of salicylic aldehyde was carried out in the presence of pyridine with azeotropic removal of water and gave rise to the complex of pyridine with B(III) (**116**), bonded to three oxygen atoms (87IZV2118; 89IZV946) [Eq. (75)].



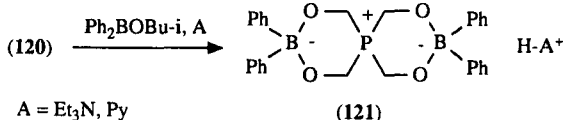
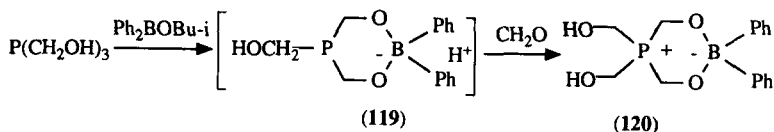
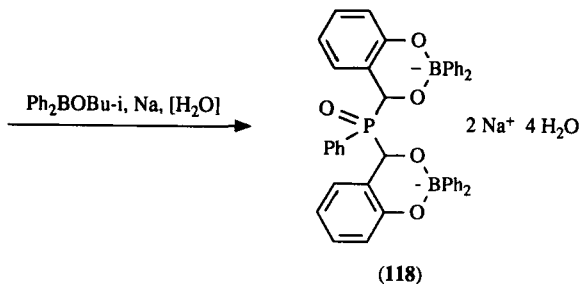
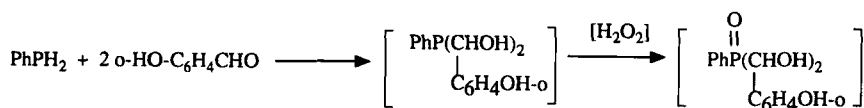
The reaction with 2 mol of diphenylboric acid ester gives rise to a diborylated product (**117**) [Eq. (76)] (89IZV946). The reaction proceeds in a similar manner when triethylamine is replaced by metallic sodium [Eq. (77)] (90IZV886).



A series of heterocycles has been obtained from tris-(hydroxymethyl) phosphine [Eq. (78)] (90IZV1133).

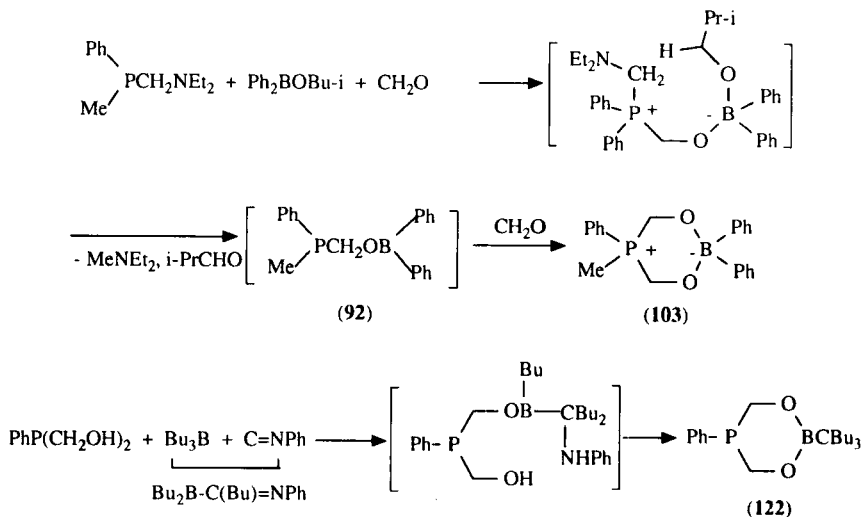
Isolation of intermediate **119** appeared to be impossible, since the formation of a more stable betaine structure (**120**) was observed. The interaction of compound (**120**) with a second molecule of boric acid ester in the presence of triethylamine or pyridine gave rise to spirobicycle **121** [Eq. (79)].

Borylation of hydroxyalkylphosphines in the absence and presence of additional reagents is the most effective and universal method of synthesizing the boroxoalkyl derivatives of phosphorus, providing a wide variety of structures. Among other methods of synthesis of boroxoalkylphosphines from aminomethylphosphines is of special interest. This is illustrated in



the case of the interaction between diethylaminomethyl(methyl)phenylphosphine and the diphenylboric acid isobutyl ester [Eq. (80)]. The reaction proceeds only in the presence of paraformaldehyde by hydride transfer and is the first example of the replacement of an amino group by the boroxymethyl group in tertiary phosphines (83IZV1926). The reaction of bis(α -hydroxyalkyl)phosphines with trialkylboranes and isonitriles are of significance as a method of synthesis of 1,3,2,5-dioxaboraphosphorinanes with branched substituents at the boron atom. Bis(α -hydroxyalkyl)phenylphosphine reacts as a proton donor, producing the migration of all the butyl groups of the intermediate iminoborane to the neighboring carbon atom with the formation of 5-phenyl-2-(1,1-dibutylamyl)-1,3,2,5-dioxaboraphosphorinane (122) [Eq. (81)] (88IZV2409; 91IZV719). The substituted phosphorus-containing diol reacted like a masked aldehyde; 2,2-dibutyl-3,4,5-triphenyl-1,3-oxazolidine evolved and phenylphosphine and phenylboric acid anhydride were obtained.

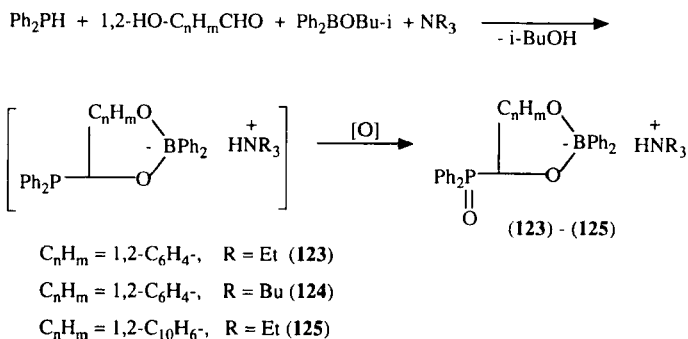
All the above structures contain the P—C—O—B fragment. Among boryloxyalkylphosphines and their derivatives with an exocyclic phosphorus containing group, (123)–(125) are reported (92IZV196). Such compounds were obtained from secondary phosphines, aromatic alde-

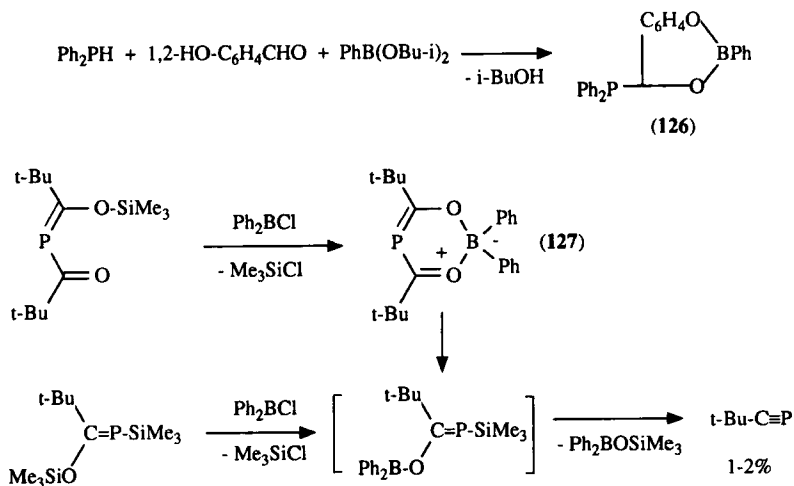


hydes containing an *ortho*-hydroxy group, and boric acid esters [Eq. (82)]. The reaction proceeded in one stage without isolation of intermediates, similar to the reaction with phenylphosphine. Attempts to isolate the corresponding compounds of tricoordinated phosphorus failed because they are easily oxidized. This fact was mentioned earlier for other boroxyalkylphosphines, obtained from salicylic aldehyde (87IZV2118; 89IZV946; 90IZV886).

More significant differences from the properties of cyclic boryloxyalkylphosphines were revealed for 5,6-benzo-4-diphenylphosphino-2-phenyl-1,3-dioxo-2-boracyclohexane (**126**), obtained by the interaction of diphenylphosphine, salicylic aldehyde, and phenylboric acid ester [Eq. (83)] (92IZV196).

The following serves as one more example of the synthesis of a P,B-containing heterocycle (**127**) with a dicoordinated phosphorus atom [Eq.





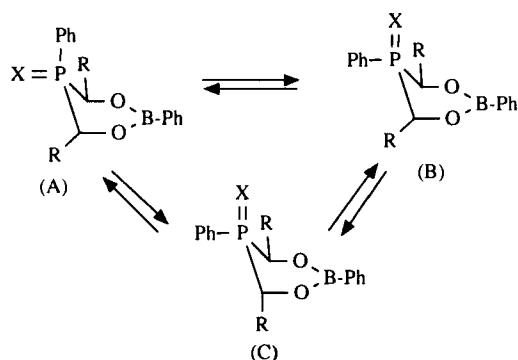
(84)] (91IZV2670, 91PS133). An X-ray single-crystal investigation showed **127** to possess C_s symmetry, with the boron atom out of the plane formed by the other five atoms.

Thus, existing methods give the possibility of obtaining various heterocyclic compounds containing the P—C—O—B fragment with phosphorus and boron atoms being in a different coordination.

B. STEREOISOMERISM OF 1,3,2,5-DIOXABORAPHOSPHORINANES

1,3,2,5-Dioxaboraphosphorinanes (**90**), (**93**)–(**97**), and their derivatives are remarkable objects for conformational studies (83MI1; 84MI1; 86MI1). The compounds were isolated in the form of separate stereoisomers whose structures were determined by ^1H and ^{31}P NMR spectroscopy and by dipole moment and X-ray analysis. In solution these compounds exist in the form of a mixture of three stereoisomers and conformers (at $R = \text{H}$), which differ by the orientation of their substituents at carbon and phosphorus [Eq. (85)]. The six-membered ring adopts a “sofa” conformation with the phosphorus atom being out of the plane of the five other atoms (79IZV2349; 83IZV1374, 83IZV2535; 84IZV2501; 88MJ1).

For 1,3,2,5-dioxaboraphosphorinanes with a tricoordinated phosphorus atom, equilibration of the stereoisomers has been observed after a few hours at 20°C without any catalyst. In the case of the sulfide and selenide the equilibrium is established in 11–20 h at 80°C in the presence of *p*-toluenesulfonic acid. The equilibrium composition of 2,5-diphenyl-4,6-



X = lone pair, O, S, Se; R = H, Me, Pr, Ph

di-*R*-1,3,2,5-dioxaboraphosphorinanes and their derivatives is presented in Table IV.

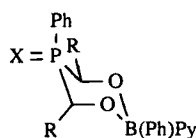
For 4,6-disubstituted dioxaboraphosphorinanes an increase in the share of the conformation with nonequivalent substituents at the carbon atoms is observed (C form). A comparison of the equilibria $A \rightleftharpoons C$ and $B \rightleftharpoons C$ indicates the C form to be more stable than form B, but less stable than

TABLE IV
EQUILIBRIUM COMPOSITION OF CONFORMERS AND
STEREISOMERS FOR 2,5-DIPHENYL-4,6-di-*R*-1,3,2,5-
DIOXABORAPHOSPHORINANES AND THEIR DERIVATIVES

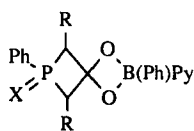
R	X	T (°C) solution	A \rightleftharpoons B	B \rightleftharpoons C	Time (h)	
H	lone pair	Benzene	96	4	0	2
Me		Reaction mixture	51	28	21	
		20°, C ₆ H ₆	25	29	19	24
		90°, xylene	46	36	18	5
		20°, MeCN	49	36	15	5
Pr		20°, C ₆ H ₆	42	24	33	144
		50°, C ₆ H ₆	44	19	37	5
		90°, xylene	37	30	33	5
		20°, Py	41	26	33	480
Ph		20°, C ₆ H ₆	73	12	15	144
		70°, C ₆ H ₆	74	13	13	4
H	S	80°, C ₆ H ₆	75	25	0	11
Me	S		41	29	30	12
Pr	S		20	0	80	16
Ph	S		0	100	0	14
Me	Se		28	17	55	20
Pr	Se		0	0	100	11
Ph	Se		0	100	0	

form A. On passing from compounds with a tricoordinated phosphorus atom to tetracoordinated one, the amount of form A in the equilibrium mixture decreased. Selenides contain smaller amounts of form A compared to sulfides.

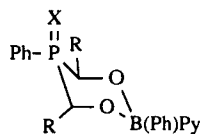
The boron atom has tetrahedral coordination in pyridine complexes of 1,3,2,5-dioxaboraphosphorinane sulfides and selenides. These compounds exist as a mixture of conformers and stereoisomers [Eq. (86)]. In some cases it appeared possible to isolate three individual stereoisomers of one substance. The chemical shift in ^{31}P NMR spectra was shown to be stereospecific.



(A)



(C)

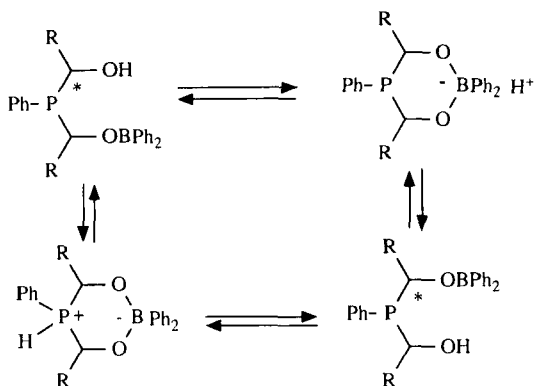


(B)

The influence of substituents at phosphorus and carbon atoms on the equilibrium position of dioxaphosphorinanes and their derivatives is due to donor-acceptor interaction. Stereospecific coupling constants are found for 4,6-disubstituted dioxaphosphorinanes and the possibility of applying them to determine the spatial structure of isomers has been reported.

C. TAUTOMERISM

Prototropic tautomerism of boryloxyalkylphosphines [83MI1; 84IZV2089; 85IZV2362; 86MI1; 90IZV1133, 90MI1, 90PS(49-50)271] is generally caused by migration of a proton among three nucleophilic centers: tricoordinated phosphorus atom and two oxygen atoms. In addition, a form with the proton close to the four-coordinated boron atom is also possible. Migration of the proton is accompanied by alteration of phosphorus and boron coordination. Thus, four forms are possible: two phosphino-boryl forms with both phosphorus and boron tricoordinated, a phosphino-borate form with tricoordinated phosphorus and a four-coordinated boron atom, and a phosphonium-borate form with four-coordinated phosphorus and boron [Eq. (87)]. Acyclic forms with the same substituents at carbon atoms are identical, reducing the total to three; this type of tautomerism is called degenerate. In the case of P(III) derivatives dissociation of the α -hydroxyalkyl fragment of the acyclic tautomeric form with the formation of aldehyde and phosphine is also possible (see Section IV,D,2).

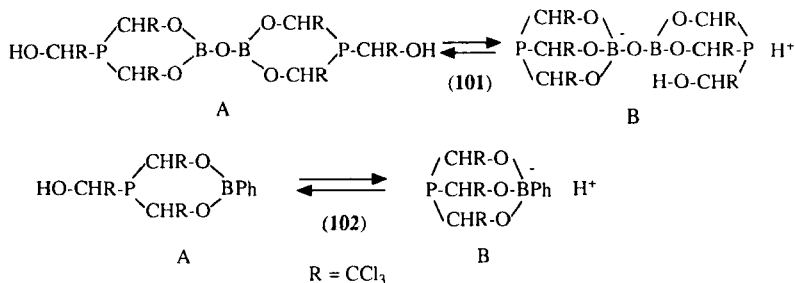


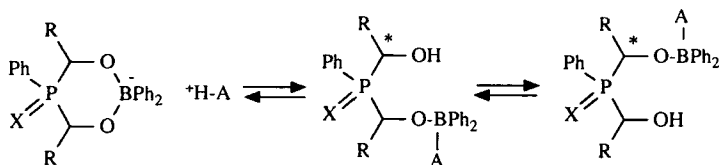
A phosphino group may be replaced by a phosphoryl, thiophosphoryl, or selenophosphoryl and a quasi-phosphonium group by a phosphonium one. Some of theoretically possible types of boryloxyalkylphosphine tautomerism have been experimentally observed.

Boryl–borate tautomerism: This type of tautomerism is observed for boryloxyalkylphosphines (**101**), (**102**) possessing a hydroxyalkyl group and electron-acceptor substituents at the α -carbon atom [Eq. (88)] (85IZV1102; 90IZV1133). Mutual transformations take place rapidly and the equivalency of methyne protons in NMR spectra serves as evidence of tautomerism. In the crystalline state these compounds exist in form A. The considerable influence of the nature of the solvent (-4 ppm in DMFA; -10 ppm in C_6H_6) on the position of the signal in the ^{31}P NMR spectrum provides evidence in favor of tautomerism.

Ion–complex tautomerism: Ion–complex tautomerism (84IZV2089; 85IZV2362, 85IZV2369; 87IZV2118, 87ZOB2639; 90IZV1133; 92ZSK133) can be generally presented by the following equilibrium [Eq. (89)]:

The ionic structure of crystalline substances is easily established by the absence of the absorption characteristic of hydroxyl groups in the range $3100\text{--}3600\text{ cm}^{-1}$ and the presence of the band at $2500\text{--}2700\text{ cm}^{-1}$, corre-





X = lone pair, O, S, Se; R = Alk, Ar; A = amines

sponding to the $\text{H}-\text{N}^+$ bond. Infrared spectra of solutions showed a mixture of two forms. The absence of changes in the IR spectra over time indicates an equilibrium. The ^1H and ^{31}P NMR spectra are the average of the two forms.

The ion-complex equilibrium position depends on the nature of the amine. This is clearly manifested in the case of triethylammonium and pyridinium 2,2,5-triphenyl-5-thio-1,3,2,5-dioxaborataphosphorinanes (**111**, $\text{R} = \text{H}$, $\text{X} = \text{S}$, $\text{A} = \text{Et}_3\text{N}$ and Py). In solution the former is mainly in an ionic form; the latter exists as a complex. The basicity of the amine is assumed to be important. Triethylamine is a stronger base than pyridine and the ionic form is stabilized. When the proton affinity is weak, the basicity in relation to the $\text{B}(\text{III})$ atom, a Lewis acid, plays an important role. This involves an equilibrium shift toward the complex. This assumption is confirmed by an easy displacement of pyridine by triethylamine. The reverse process demands more severe conditions. In the NMR spectra of the triethylamine complex the signal is shifted from 22 to 42 ppm as pyridine is added. The absence of signals of two separate forms is evidence in favor of their fast interconversion. The chemical shift of the signal in ^{31}P spectra is 22 ppm (EtOH), 26 ppm (Py , DMFA), and 42 ppm (EtOH , Py) for complexes with triethylamine and pyridine.

On studying a series of ammonium 1,3,2,5-dioxaborataphosphorinane oxides (**111**), the dependence of the tautomeric equilibrium position on amine basicity was analyzed. The equilibrium position was estimated from chemical shift values of bis(oxymethyl)phenylphosphine oxide with $\delta^{31}\text{P}$ of 35 ppm being used as a model of an acyclic form and 5-Ph-5-oxo-1,3,5-dioxaphosphorinane (**107**, $\text{R} = \text{H}$) with $\delta^{31}\text{P}$ of 6 ppm used as a model of a cyclic compound. The chemical shift values (**111**, $\text{X} = \text{O}$, $\text{R} = \text{H}$) and dissociation constants (pK_a) of conjugate acids for amines are presented in Table V.

As seen in Table V, there is a clear dependence of the equilibrium position on the basicity of amines, excluding triethylamine. However, it is necessary to take into account not only the proton affinity of the amine, but also the ability of the amine to form a dative bond with a boron atom. The equilibrium position also depends on the structure of the phosphorus-

TABLE V
 ^{31}P CHEMICAL SHIFTS OF (111) AND pK_a VALUES OF THE
 CONJUGATE ACIDS OF AMINES

Amines ^c	$\delta \text{ } ^{31}\text{P}$ (ppm)	pK_a^a	Remarks
Pr_2NH	27	10, 93	For Et_2NH
$t\text{-C}_8\text{H}_{17}\text{NH}_2$	27	10, 65	For $n\text{-C}_8\text{H}_{17}\text{NH}_2$
$\text{HO}(\text{CH}_2)_4\text{NH}_2$	27	—	
$(\text{C}_5\text{H}_{11})_2\text{NH}$	29	—	
$t\text{-BuNH}_2$	29	10, 45	
$\text{EtN}(\text{CH}_2)_5$	29	10, 08	For $\text{MeN}(\text{CH}_2)_5$
$\text{HSCH}_2\text{CH}_2\text{NH}_2$	29	—	
$\text{HOCH}_2\text{CH}_2\text{NH}_2$	29	9, 50	
Et_3N	32	10, 87	
$p\text{-MeC}_6\text{H}_4\text{NH}_2$	34	5, 12	
Py	35	5, 23	
$p\text{-MeOC}_6\text{H}_4\text{NH}_2$	36	5, 29	
$m\text{-Amino benzoic acid}^b$	—	3, 12	
Ph_2NH^b	—	0, 9	

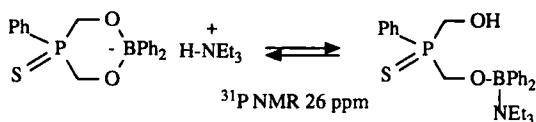
^a Albert and Sergent (64M11).

^b Amines, which do not form complexes.

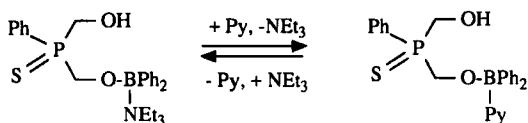
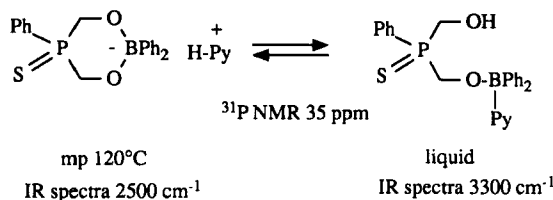
containing fragment. Stronger inductive effects of thio and seleno phosphoryl groups stabilize the ionic form. The phosphoryl group forms hydrogen bonds with the hydroxyl group and shifts the equilibrium toward the complex. The difference between the tri- and the tetra-coordinated phosphorus derivatives is especially evident as far as the possibility of forming products with an amine is concerned. Complexes with pyridine are easily formed for P(IV) derivatives, but not for P(III). This may be connected with the weaker electron-acceptor ability of the phosphine group.

Both forms have been isolated in a number of cases [Eq. (90)]. The ionic component has been obtained when diphenylboryloxymethyl(oxy-methyl)phenylphosphine sulfide is treated with triethylamine or pyridine. In the case of pyridine the complex is isolated by careful evaporation of benzene solvent. Unlike the ionic form, which is crystalline, the complex form is a liquid. In its IR spectrum there is an intense absorption of the hydroxyl groups and no absorption of the $\text{H}-\text{N}^+$ bond. Spectra of benzene solutions of the complex and ionic forms are identical. With crystallization the complex form rearranges into the ionic form.

Thus, ion-complex tautomerism occurs when the cyclic form is transformed into the acyclic form. In this case the rupture of two bonds and the formation of two new ones occur. All the atoms retain their coordination; only the type of bonds changes. Redistribution of electronic density



IR spectra 2500, 2600 cm^{-1}

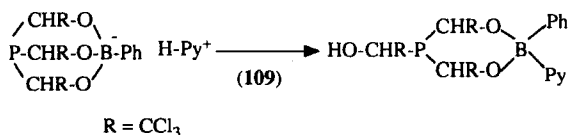


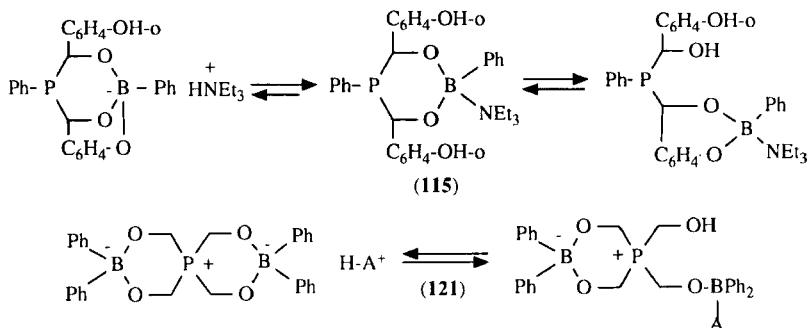
results in either the complex or the ionic form. Herein lies the difference from the commonly observed ring-chain tautomerism where proton transfer does not involve the formation of a dissociable ionic form. Moreover, there are two migrating particles, hydrogen and nitrogen atoms.

Bicyclic–monocyclic ion–complex tautomerism: The introduction of functional groups onto the substituent at carbon, nitrogen, or phosphorus atoms increases the number of possible types of ion–complex tautomerism. For example, the presence of one more hydroxyalkyl group at the phosphorus atom results in bicyclic–monocyclic tautomerism [Eq. (91)] (85IZV469, 85IZV1102; 89IZV946).

The crystalline compound (**109**) exists in a bicyclic form, as determined by X-ray analysis. In benzene solution absorption of an hydroxyl group appears. At the same time all three methine protons in the ^1H NMR spectra are equivalent and in the ^{31}P NMR spectrum there is only one signal.

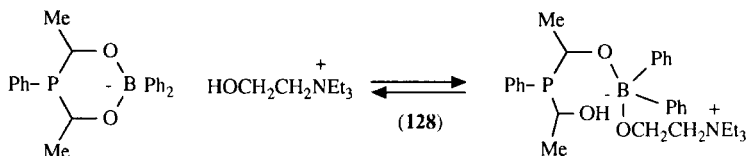
Functional groups in the substituent at the carbon atom can take part in the formation of new tautomeric forms, as in **115**, [Eq. (92)] (87IZV2118; 89IZV946; 90IZV1133). Infrared spectra of **121** in solvent contain absorption bands for the hydroxyl groups and the $\text{N}^+ - \text{H}$ fragment, the former





being absent in the spectra of crystals. An averaged methylene proton signal is observed in ^1H NMR spectra. Thus, two forms take part in the tautomeric equilibrium [Eq. (93)] (90IZV1133).

Ion-ion tautomerism: Functional groups with a mobile hydrogen atom present in the ammonium cation can result in one more type of tautomerism, as in the case of β -oxyethyl(triethyl)ammonium 1,3,2,5-dioxaborataphosphorinane (**128**) (88IZV155). In this case the equilibrium between two ionic forms (acyclic and cyclic) has been observed [Eq. (94)].



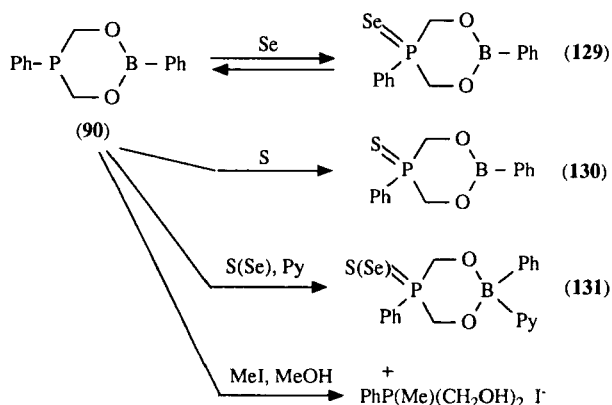
Both ionic forms have the same set of characteristic bands in their IR spectra and thus cannot be identified in solution. The ^{31}P NMR spectrum contains only one averaged signal. The IR study revealed tautomeric transformations in solution. The characteristic absorption band of the P—H bond and carbonyl group appeared in solution spectra; that is possible only on dissociation of the α -hydroxyalkyl fragment, present only in the second tautomeric form. An X-ray single-crystal study showed the compound (**128**) to be in a cyclic form.

D. REACTIONS

Chemical properties of boroxalkyl derivatives of phosphorus are determined by the type of P—C—O—B system, by the presence of a mobile hydrogen atom, by the coordination of phosphorus and boron atoms, and by the type of substituents at phosphorus [84MI1; 86MI1; 87MI1; 89MI1; 90MI1, 90PS(49-50)271; 92UK616, 92ZSK133]. Reactions with electro-

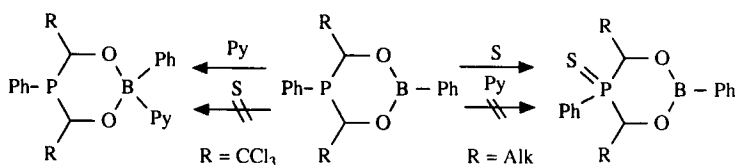
philic reagents are characteristic of these structures. There are two centers for electrophilic attack—phosphorus and oxygen atoms, and there is a ring carbon atom and a tricoordinated boron atom, capable of reacting with nucleophilic reagents. The presence of a donor (phosphorus) and an acceptor (boron) in a molecule at the same time makes possible reactions with compounds possessing a polarized multiple bond (aldehydes, nitriles). This involves displacement of the C—O fragment from the P—C—O—B system by aldehydes. Ion exchange reactions are characteristic of ammonium 1,3,2,5-dioxaborataphosphorinanes. Some types of boroxalkylphosphines can involve thermal conversions.

However, the most interesting feature is the dependence of the reactivity of one center on the state of another (phosphorus and boron atom), which bears evidence about the interaction between the heteroatoms in the P(III)—C—O—B(III) system. This interaction stabilizes the compounds; i.e., it leads to the lowering of their reactivity in contrast to that of the individual tertiary phosphines and boric acid derivatives. Thus, 2,5-diphenyl-1,3,2,5-dioxaboraphosphorinane (**90**) is not oxidized in air, is inert to methyl iodide, slowly interacts with sulfur (reactions at the phosphorus atom), does not form any complex with pyridine, and does not undergo hydrolysis with aqueous methanol (reactions at the boron atom). The simultaneous effect of reagents on both phosphorus and boron atoms facilitates reactions. In fact, the addition of sulfur proceeds exothermically in pyridine, with the formation of its complex (**127**), the corresponding phosphine sulfide. Phosphonium salts are easily obtained in reactions with methyl iodide in methanol, etc. [Eq. (95)] [83IZV2545, 83MI1; 87MI1; 90PS(49-50)271]. Thus, the reactivity of the phosphorus atom depends on the coordination of the boron atom and vice versa. The larger content of the isomer with the axial substituent at phosphorus in



the stereoisomeric equilibrium mixture of 1,3,2,5-dioxaboraphosphorinanes or their derivatives in contrast to 1,3,5-dioxaphosphorinanes can also be explained in terms of intramolecular phosphorus–boron interactions.

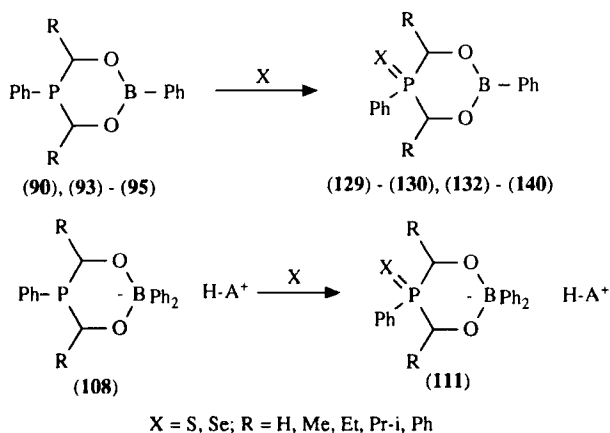
This intramolecular interaction of heteroatoms may be distorted by introducing different substituents onto the 4,6-positions of the ring. In the case of acceptor substituents, (CCl_3) dioxaboraphosphorinane (**97**) is not alkylated at the phosphorus atom and is inert to sulfur; at the same time it forms a stable complex with pyridine [Eq. (96)]. In the case of donor substituents (Alk) (**93**)–(**94**), by contrast, the corresponding sulfides have been obtained and the pyridine complex is formed only with four-coordinated phosphorus derivatives.

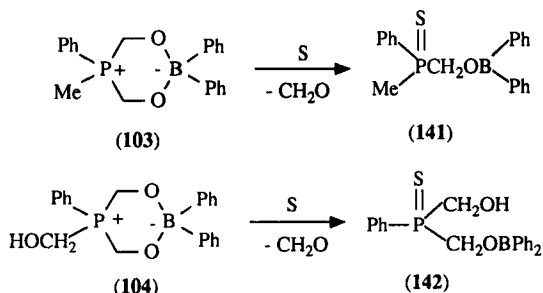


1. Reaction with Electrophilic Reagents

Boryloxyalkylphosphines (**90**), (**93**)–(**95**) interact with elemental sulfur and selenium as ordinary phosphines [Eq. (97)]. Except for the above-mentioned examples, the reaction proceeds as usual with the formation of the corresponding sulfides and selenides (80IZV1438; 83IZV2535, 83MI1; 84IZV2089, 84UK625; 85IZV2359; 86MI1; 90MI1; 92IZV1398).

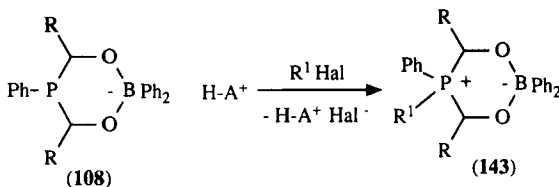
Sulfides (**111**) can be obtained by the interaction of sulfur with betaines (**103**), (**104**) [Eq. (98)] (80IZV1438; 84IZV2089). Such reaction is not typical to phosphonium derivatives of oxyalkylphosphines.





Reactions with electrophilic reagents are most characteristic of ammonium 1,3,2,5-dioxaborataphosphorinanes (**108**) [87MI1; 88IZV155; 90PS(49-50)271; 92IZV1398] readily proceeding with halogen-containing reagents in particular. Several reactions are possible. The attack of electrophilic reagents at the phosphorus atom results in the formation of 1,3,2,5-dioxaborataphosphoniarinanes (**143**), whereas the attack at the oxygen atom leads to acyclic oxyalkylphosphine derivatives. The third direction gives rise to new 1,3,2,5-dioxaborataphosphorinanes, if the positive electrophilic center is able to exist as a cation.

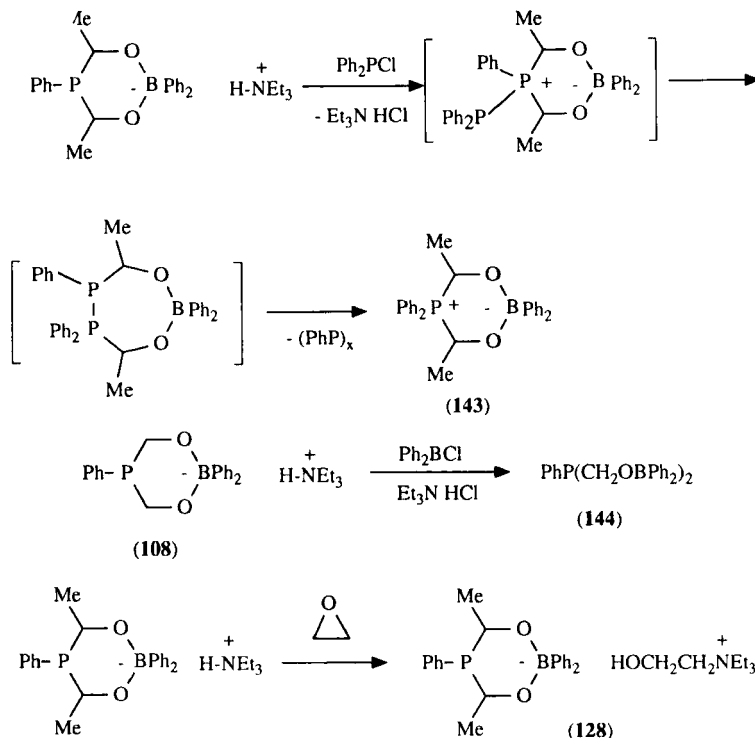
The first pathway is realized in the reaction with alkyl halides and gives betaines [Eq. (99)].



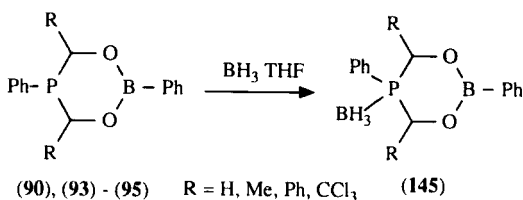
These reactions may be considered to be a method of obtaining 1,3,2,5-dioxaborataphosphoniarinanes with different substituents at carbon and phosphorus atoms of the ring. Comparing the properties of cyclic oxyalkylphosphines and boryloxyalkylphosphines, it should be noted that in both cases the reaction with alkyl halides results in the formation of a tertiary phosphonium salt. The reaction with electrophilic reagents such as diphenylchlorophosphine and diphenylchloroborane proceeded quite differently [Eq. (100)].

Another reaction was observed for diphenylchloroborane [Eq. (101)].

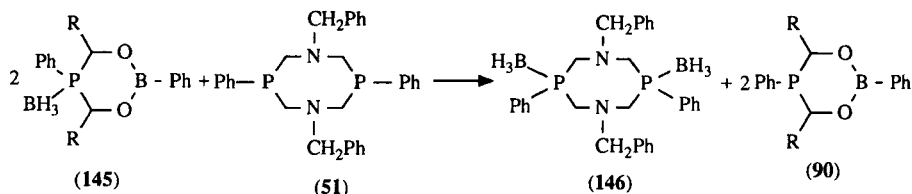
One more reaction route was shown for the interaction with ethylene oxide [Eq. (102)]. In the present case, one could expect the substitution of the α -oxyalkyl fragment of boryloxyalkylphosphine by β -oxyalkylphosphine, as observed for α -oxyalkylphosphines (88IZV155).



Complexes with borane can be obtained due to the presence of the tricoordinated phosphorus atom [Eq. (103)] (90IZV1120). When heated



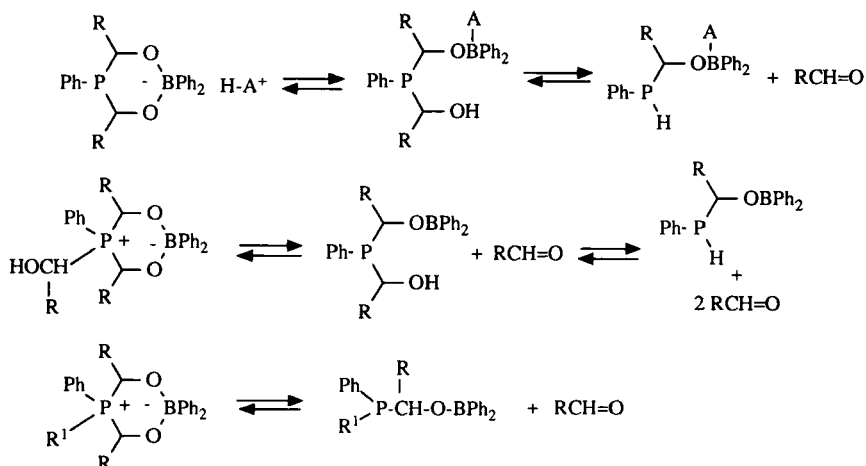
in organic solvents (acetone, chloroform, methanol, dimethylformamide) 1,3,2,5-dioxaboraphosphorinane complexes with borane (145) decompose back into their precursor compounds. Moreover, reductive cleavage of the P—C and C—O bonds in the P—C—O—B fragment is not observed even in the presence of electron-acceptor substituents. The low stability of the 1,3,2,5-dioxaboraphosphorinane complexes with borane (145) in solution makes it possible to use them as borylation reagents [Eq. (104)]. In fact, these complexes with 1,5,3,7-diazadiphosphacyclooctane (51) give rise to the diazadiphosphacyclooctane complex (146) with two borane molecules in 80% yield.



The migration of borane from the phosphorus atom in 1,3,2,5-dioxaboraphosphorinane to the phosphorus atom in 1,5,3,7-diazadiphosphacyclooctane is evidence of a lower phosphorus nucleophilicity in the P(III)—C—O—B(III) system than in the P—C—N fragment, which may result from the phosphorus–boron interaction in 1,3,2,5-dioxaboraphosphorinane (90IZV1120).

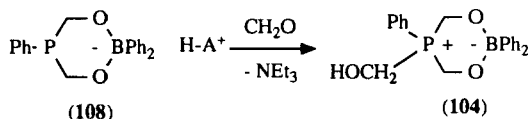
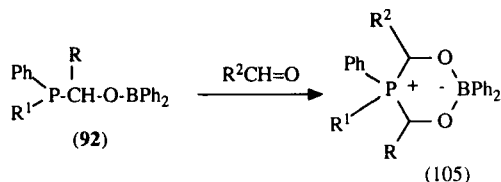
2. Reactions with Bipolar Reagents

One of the properties of α -hydroxyalkylphosphines is their ability to dissociate in solution to give aldehyde and phosphine. The same property is typical to boryloxyalkylphosphines [Eq. (105)]; however, unlike α -hydroxyalkylphosphines the dissociation is possible also for cyclic compounds (86IZV2502, 86IZV2510; 90IZV1133).



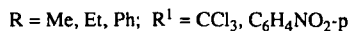
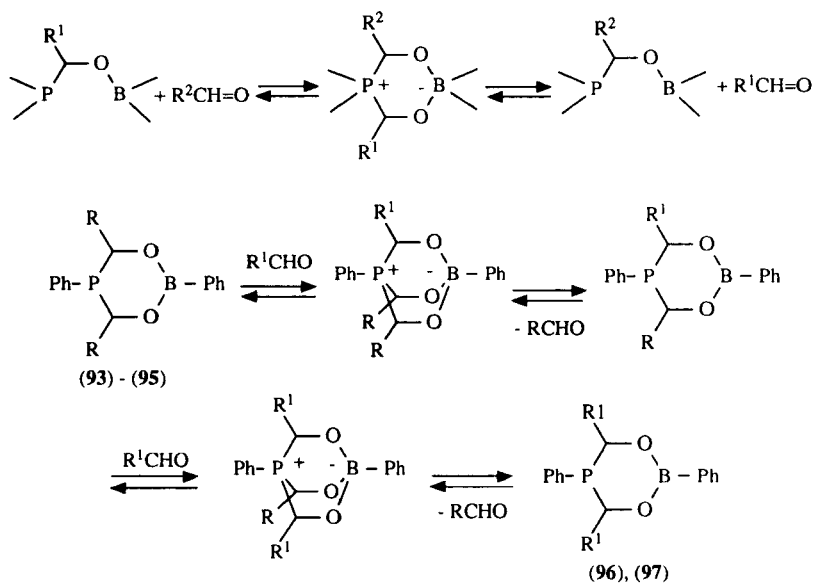
Due to the ability of phosphorus and boron atoms to change their coordination reversibly, they can undergo reactions with bipolar reagents such as aldehydes and nitriles.

The addition reaction with aldehydes, taking place with the participation of the P(III)—C—O—B(III) fragment, results in the formation of ring betaines [Eq. (106)] (83IZV2541; 86IZV2510; 90IZV1133; 92IZV1398).



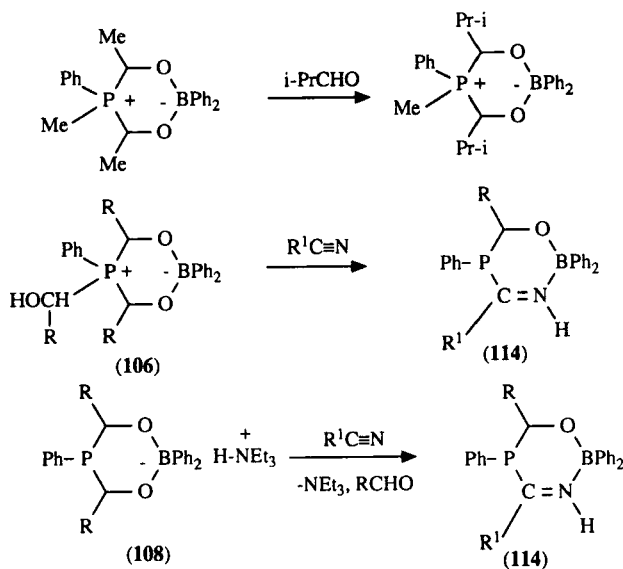
Betaines may be considered to be the intermediate products in the displacement of the C—O fragment from the P—C—O—B system, whereas the addition of aldehydes to the P—C—O—B system constitutes the first stage. This reaction is due to the fact that phosphorus and boron atoms can change their coordination reversibly and convert into the tetra-coordinated state. The displacement of one aldehyde by another is carried out in a solvent or in excess aldehyde. In general this reaction is represented by the following scheme [Eq. (107)].

The formation of substitution products of aldehyde fragments was observed during the interaction of substituted 2,5-diphenyl-1,3,2,5-dioxabor-

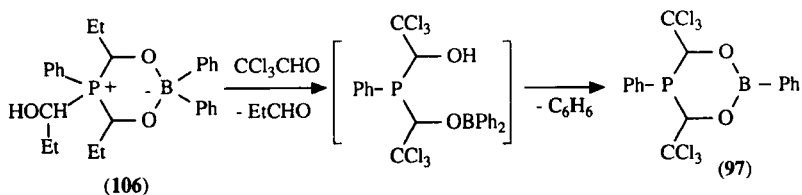


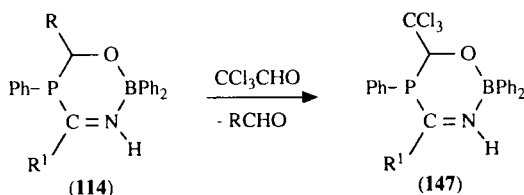
aphosphorinanes with aldehydes [Eq. (108)]. The reaction involves several stages (84MI2).

The C—O fragments separating phosphorus and boron atoms in dioxaborataphosphoniarinanes are substituted when treated by aldehydes or nitriles. In this case the displacement of aldehyde fragments occurs through the initial dissociation of betaines into compounds with tricoordinated phosphorus and boron atoms [Eq. (109)] (86IZV2502, 86IZV2510).

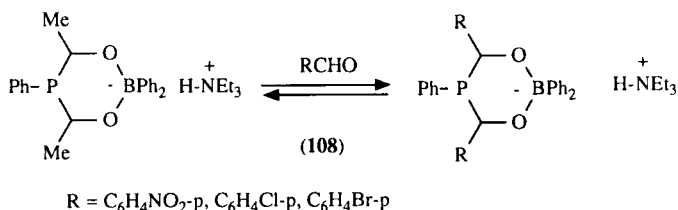


When 1,3,2,5-dioxaborataphosphorinane with the α -hydroxyalkyl group is exposed to an excess of chloral, the substitution of fragments between phosphorus and boron atoms is followed by the elimination of benzene [Eq. (110)] (86IZV2502). An excess of chloral affects diphenylboryloxyalkyl(imido)phosphine, just as in the case of dioxaboraphosphorinanes, resulting in substitution products [Eq. (111)] (86IZV2510). The above reaction makes it possible to obtain imido)phosphines that are inaccessible by borylation of bis(α -oxy- β,β,β -trichloroethyl)phenylphosphine.





Substitution of the fragment separating phosphorus and boron atoms have also been described for ammonium 1,3,2,5-dioxaborataphosphorinanes [Eq. (112)] (86IZV2502, 86IZV2510; 92IZV1398).



When examining the mechanism of these reactions, it is necessary to consider ion-complex tautomerism and the fact that reactions can proceed through dissociation of α -hydroxyalkyl fragments to the secondary phosphine and aldehyde.

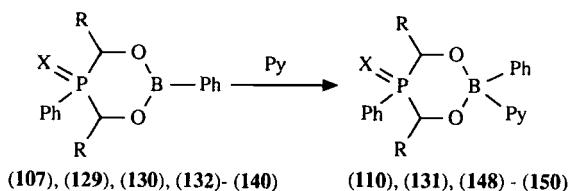
3. Reactions with Nucleophilic Reagents

Boryloxyalkylphosphines and their derivatives contain two centers available for nucleophilic attack—the carbon atom bonded to phosphorus and the tricoordinated boron atom. Primary, secondary, and tertiary aromatic amines and pyridine were used as nucleophilic reagents [79IZV2771; 80IZV721, 80IZV2129, 80MI2, 80MI3; 83MI1; 84MI1; 86MI1; 90MI1, 90PS(49-50)271].

The derivatives of cyclic boryloxyalkyl phosphines readily undergo complexation with tertiary amines and especially pyridine with the participation of the boron atom [Eq. (113)] (83IZV2545; 86IZV643).

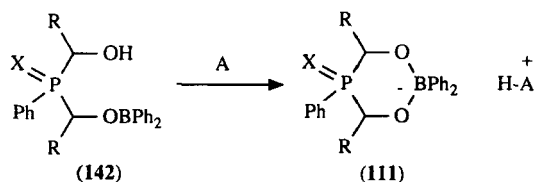
Tertiary amines or pyridine reacts with diphenylboryloxyalkyl(α -oxyalkyl)phenylphosphine sulfide to give the corresponding ammonium dioxaborataphosphorinanes [Eq. (114)] (83IZV2545). Ammonium dioxaborataphosphorinane was obtained by refluxing betaine **104** in triethylamine [Eq. (115)] (92IZV1398).

Thus, unlike α -oxyalkylphosphines, which are inert to tertiary amines, boryloxyalkylphosphines and their derivatives form addition products with participation of the boron atom.

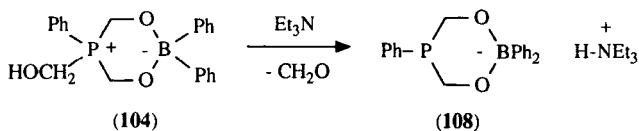


X = O, S, Se; R = Alk, Ph

X = Lone pair; R = CCl₃, C₆H₄NO₂-p



X = O, S, Se; R = Alk, Ar; A = Et₃N, Py



Different reactions are observed if primary and secondary amines are used. As a rule cyclic and acyclic aminomethyl phosphine derivatives are formed [Eq. (116)] (79IZV2771; 80IZV735, 80IZV952, 80IZV2129).

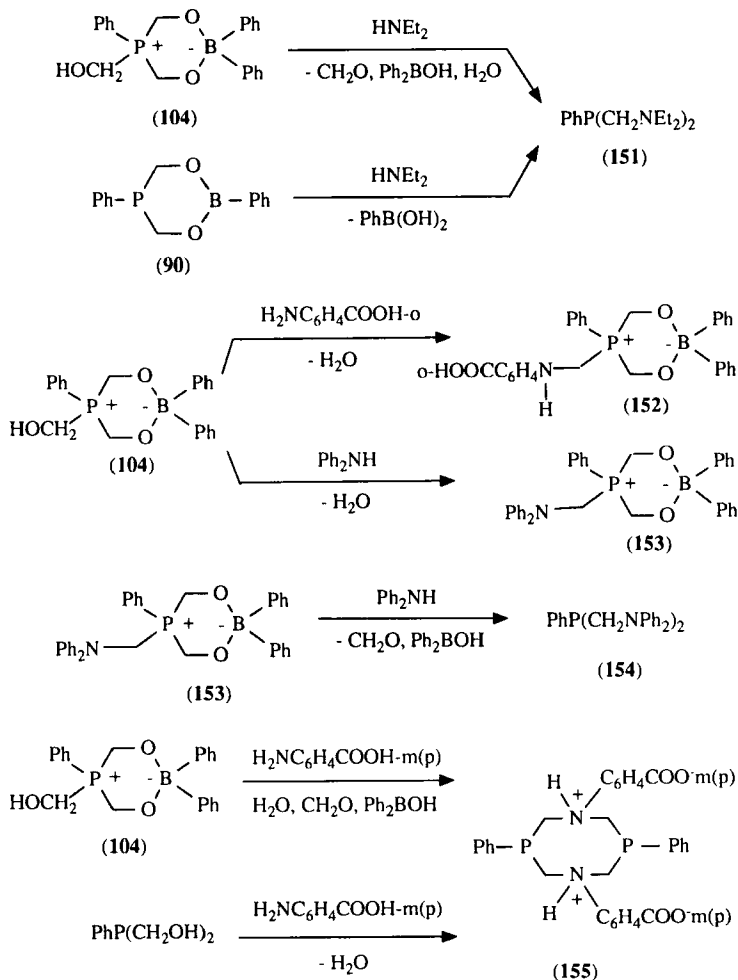
Different reactivity of α -oxyalkyl and boryloxyalkyl fragments was revealed in reactions with amines of weak basicity. For example, in the reaction with diphenylamine or *o*-aminobenzoic acid with a reagent ratio of 1 : 1, substitution of the oxymethyl group by the aminomethyl one takes place [Eq. (117)]. The P,B-containing heterocycle is retained (89IZV1340).

The reaction proceeds further on refluxing **104** with a second equivalent of diphenylamine [Eq. (118)].

The reaction with *m*- and *p*-aminobenzoic acids results in the formation of 1,5,3,7-diazadiphosphacyclooctane (**155**), possessing the structure of a double betaine [Eq. (119)]. These compounds were obtained from bis(hydroxymethyl)phenylphosphine (89IZV1340).

It should be noted that *o*-amino benzoic acid is inert to bis(oxymethyl)-phenylphosphine and 2,5-diphenyl-1,3,2,5-dioxaboraphosphorinane (**90**) (89IZV1340).

The most typical reaction is the formation of aminomethylphosphines from boryloxyalkylphosphines when treated with amines. In this respect, P,B-containing heterocycles are similar to α -oxyalkylphosphines. As

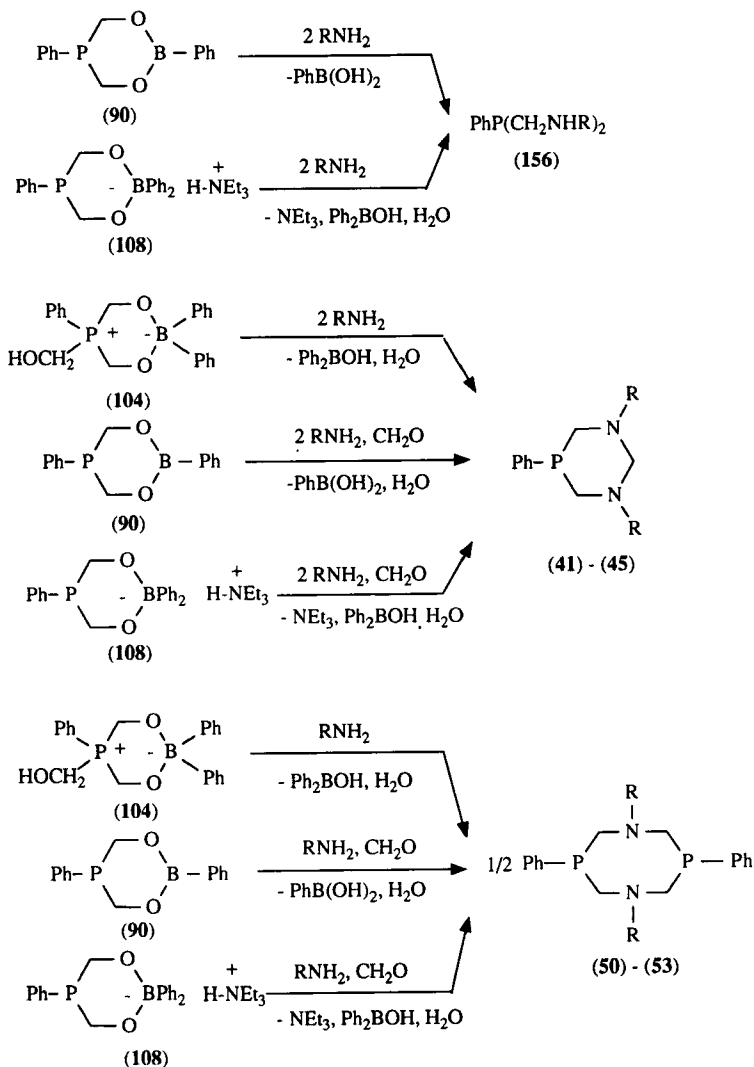


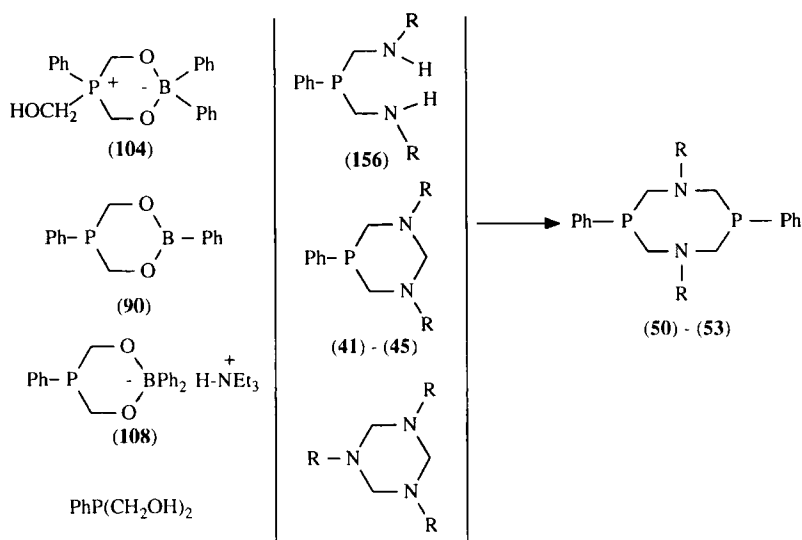
shown earlier for α -oxyalkylphosphines, reactions with amines result in individual compounds only in the case of B-containing hydroxymethyl derivatives. For alkyl derivatives, polymeric substances, which are very difficult to isolate and identify, are obtained. In the case of acceptor substituents resin formation takes place. As precursors of aminomethylphosphines, cyclic boryoxyalkylphosphines are preferable over α -hydroxyalkylphosphines. Most of the former are stable individual crystalline substances, whereas the latter are easily oxidized viscous liquids, which are difficult to purify.

The type of aminomethylphosphine derivatives formed depends on the reagent ratio, the presence of formaldehyde, substituents at the nitrogen

atom, solvent, and reaction conditions [Eq. (120)] [79IZV2771; 80IZV721, 80IZV2129, 80MI2, 80MI3; 83MI1; 84MI1; 86MI1; 90MI1, 90PS(49-50)271].

There are many examples of diazadiphosphacyclooctane formation, based on P,B-containing heterocycles and aminomethylphosphines [Eq. (121)]. 1,5,3,7-Diazadiphosphacyclooctanes are the most stable compounds in the series of aminomethylphosphines. All reactions of primary phosphines result in the formation of these heterocycles.





Thus, the reactivity of cyclic boryloxyalkylphosphines toward nucleophilic reagents (amines) is quite similar to that of α -hydroxyalkylphosphines. So, one can compare the chemical behavior of compounds with $\text{P}-\text{C}-\text{O}-\text{B}$ and $\text{P}-\text{C}-\text{O}-\text{H}$ fragments.

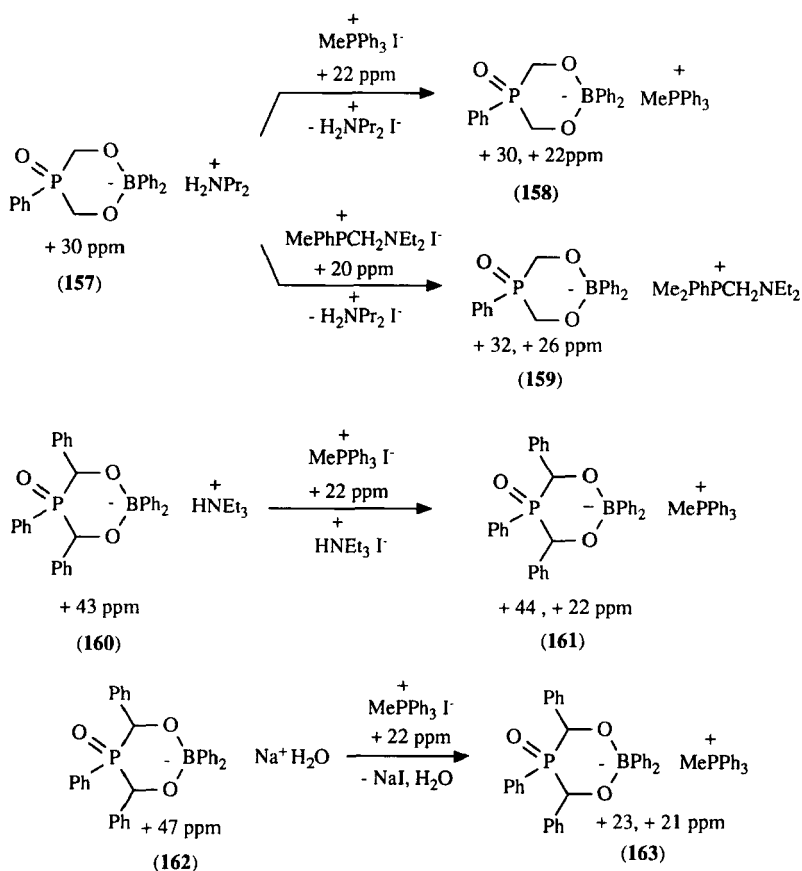
4. Ion Exchange Reactions

The ability of ammonium 1,3,2,5-dioxaborataphosphorinanes to dissociate in solutions makes it possible to carry out ionic exchange reactions. These reactions are reversible; their direction depends on solubility of the substances and their extraction from the reaction in a two-phase system consisting of organic solvent and water. Using this method compounds containing a phosphorus atom in both the cation and the anion portions—phosphonium 1,3,2,5-dioxaborataphosphorinanes (**158**), (**159**), (**161**)—were obtained [Eq. (122)] (88IZV2425, 88IZV2607; 92IZV1398).

Assignment of the NMR signal was made comparing ^{31}P chemical shifts of initial and final compounds.

In addition to ammonium dioxaborataphosphorinanes, metallic derivatives of phosphorus containing esters of boric acids (**162**) are also able to participate in ion exchange reactions [Eq. (123)].

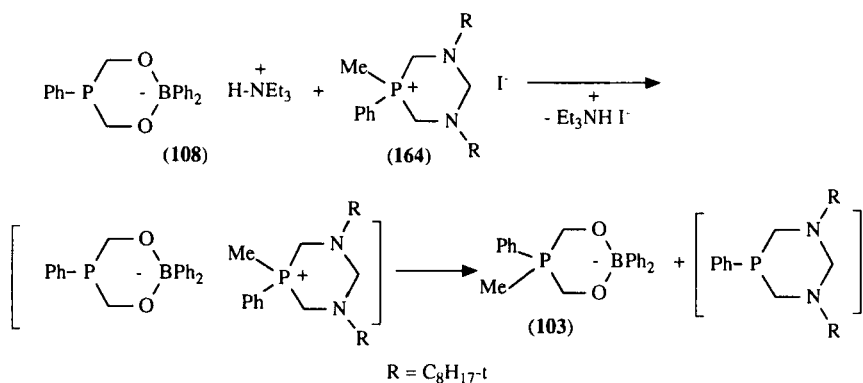
Notably, **161** and **163** have different ^{31}P chemical shift values. The anions of these molecules have different spatial structures. A ^1H and ^{31}P NMR study showed that the anion of **161** adopts a twist conformation, whereas **163** exists in a chair conformation with an equatorial phenyl at the phosphorus atom. Thus, ion exchange reactions are stereospecific.



Sometimes more complicated ion exchange reactions are observed, especially when the cation and the anion are able to interact with one another. Then, further transformations of tricoordinated phosphorus derivatives into ammonium 1,3,2,5-dioxaborataphosphorinanes are observed [Eq. (124)].

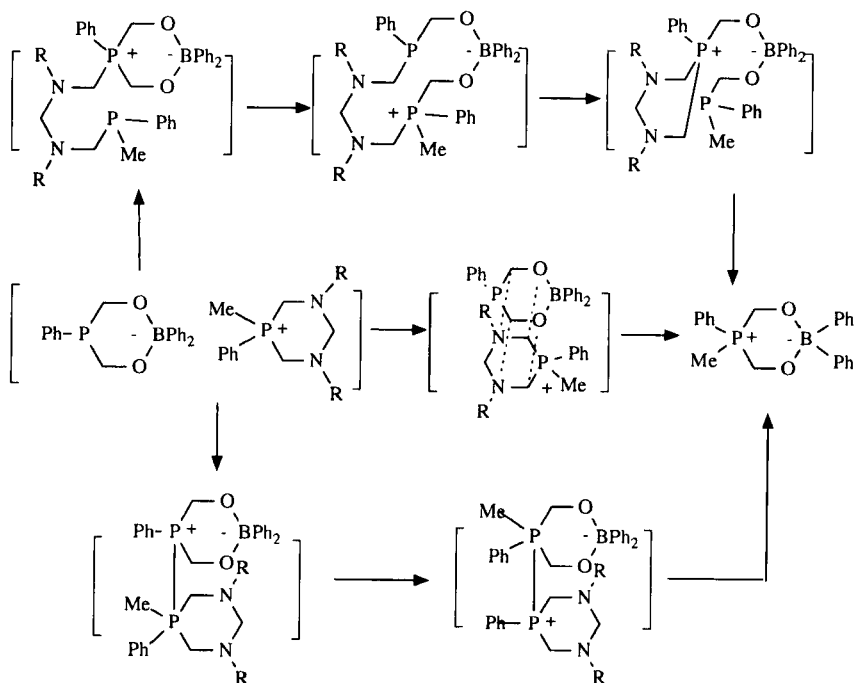
The second stage of the reaction is of particular interest. It is essentially an intramolecular reaction between the anion and the cation. The phosphorus atom of the anion is able to react nucleophilically at the ring carbon atom with amines similar to reactions of 1,3,2,5-dioxaborataphosphorinanes with amines or 1,3,5-diazaphosphorinanes. The cation is the 1,3,5-diazaphosphorinane derivative. Thus, the reaction between the anion and the cation is a series of nucleophilic attacks of nitrogen atoms, belonging to the cation, at carbon atoms of the anion.

However, other reaction directions via the formation of the phosphorane structure with migration of the methyl anion from one phosphorus atom

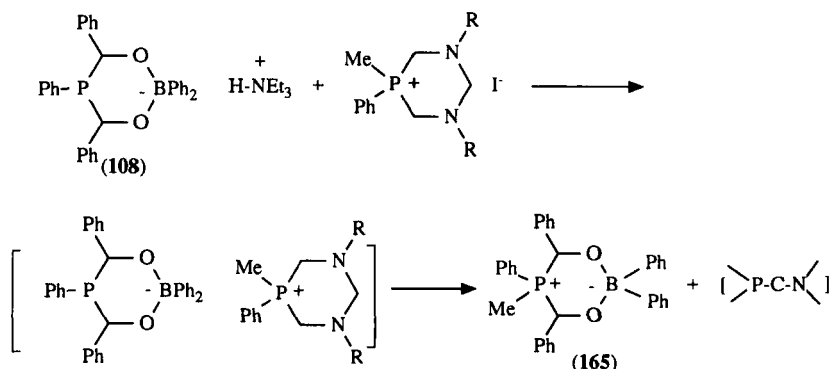


to another or via a series of nucleophilic substitutions at the α -carbon atom with the rupture of P—C bonds are possible [Eq. (125)].

The formation of the stable betaine system $\text{P}^+-\text{C}-\text{O}-\text{B}^-$ is the driving force for this reaction. With 4,6-disubstituted ammonium 1,3,2,5-dioxaborataphosphorinanes (108), there is the possibility of making a choice between two reaction directions. The reaction product formed by the phosphorane transition state, as 1,3,2,5-dioxaborataphosponiarinane



165, and bearing substituents at 4,6-positions was isolated. In the second case a 4,6-disubstituted 1,3,5-diazaphosphorinane and a 1,3,2,5-dioxaborataphosphorinane without any substituents at ring carbon atoms should be formed [Eq. (126)].



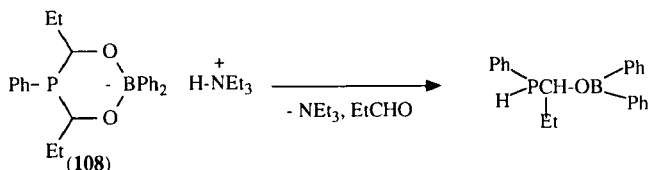
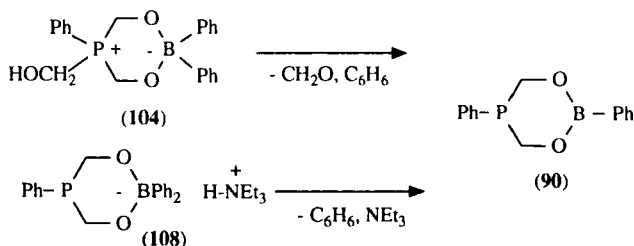
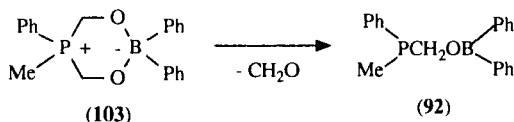
Ion exchange reactions of ammonium 1,3,2,5-dioxaborataphosphorinanes allow the possibility of synthesizing phosphonium salts containing phosphorus and boron. In these reactions anions of organic salts may be substituted by the 1,3,2,5-dioxaborataphosphorinane ring, giving a method of introducing P,B-containing fragments into medically and biologically important compounds. The presence of a reactive hydrogen atom in the phosphonium dioxaborataphosphorinanes cation results in ion-complex tautomerism with participation of the phosphorus atom.

5. Thermal Transformations

Most cyclic boryloxyalkylphosphines and their analogues are stable crystalline substances; some of them may be heated at reflux under a vacuum. At the same time further transformations may be observed on heating. Above the melting point, two processes may be observed: elimination of an aldehyde or of a benzene molecule [Eq. (127)] (79IZV2349; 88IZV155).

For ammonium 1,3,2,5-dioxaborataphosphorinanes containing alkyl substituents at a ring carbon atom, another way of decomposition on heating was observed [Eq. (128)].

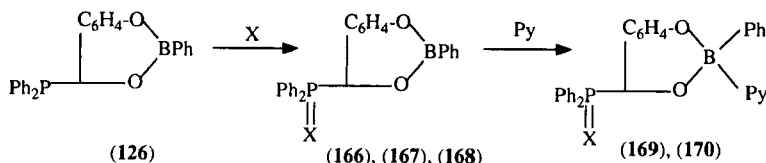
Thus, unlike α -oxyalkylphosphines and their derivatives, which undergo an oxidative rearrangement on heating, P,B-containing heterocycles are transformed into compounds with tricoordinated phosphorus and boron atoms.



6. Chemical Properties of Compounds with the P—C—O—B Fragment and Exocyclic Phosphine Group (92IZV196)

Molecule **(126)** possesses an unusual chemical shift in its ^{31}P NMR spectrum (δ ^{31}P 12.5 ppm in THF, C_6H_6 , DMFA), significantly different from that of similar tertiary phosphines, eg., diphenylbenzylphosphine (−10 ppm) and oxymethyldiphenylphosphine (−14 ppm). However, the chemical shift of compound **126** in pyridine is −4 ppm. An analogous effect was described for borylphosphine ethene (see Section V); here an intramolecular dative P—B bond is cleaved in pyridine due to the formation of complex. The chemical shift changes from 10 ppm to −4 ppm.

So, this fact is strong evidence in favor of the intra- and inter-molecular dative P—B bond in **126**. In solution, **126** is easily oxidized and undergoes addition reactions with sulfur and selenium, with the formation of the corresponding oxide (**166**), sulfide (**167**), or selenide (**168**) [Eq. (129)]. The ^{31}P chemical shifts of other compounds (**166**) (27 ppm), (**167**) (47 ppm), and (**168**) (46 ppm) are close to that observed for their structural analogues. These data and the values of dipole moments of 4.3 and 4.5 D for **166** and **167**, respectively, make it possible to exclude the formation of intramolecular dative P—B bonds similar to those observed for borylphosphine ethene

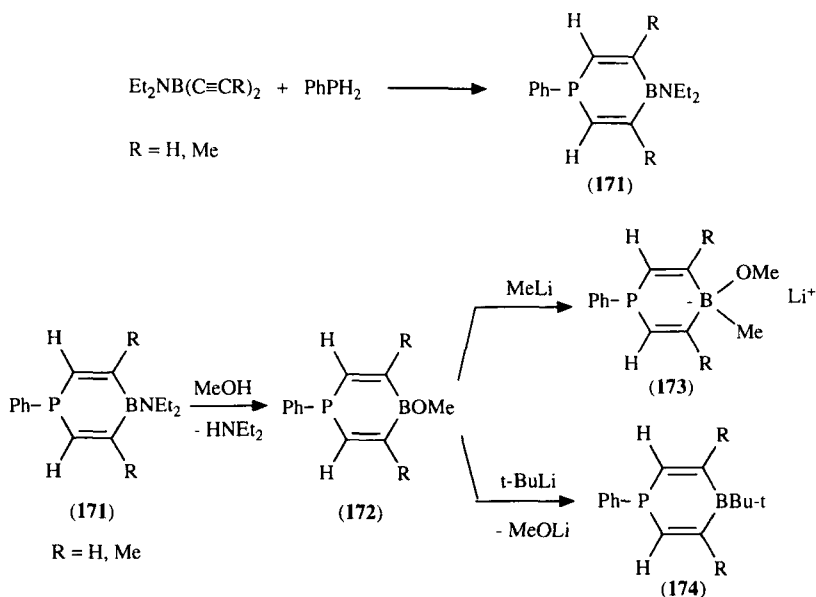


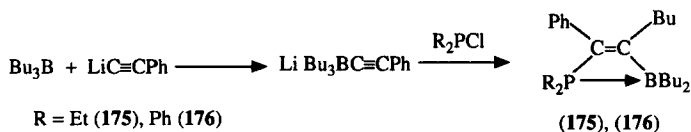
derivatives. Moreover, oxide **166** and sulfide **167** form complexes **169** and **170** with pyridine on participation of the boron atom. No significant changes of chemical shifts in ^{31}P NMR spectra and no absorption at 1360 cm^{-1} assigned to a $\text{B(III)}\text{---O}$ bond vibration, present in the IR spectra of **166** and **167**, are observed. These changes prove the presence of a four-coordinated boron atom in these complexes.

The reactivity of **126** toward electrophilic and nucleophilic reagents has more in common with borylphosphinoethenes than with 1,3,2,5-dioxaboraphosphorinanes, more evidence in favor of the existence of a weak $\text{P}\text{---B}$ dative bond. However, unlike borylphosphinoethenes, **126** is inert to molecules containing polar multiple bonds such as aldehydes, isocyanates, isothiocyanates, and thiocyanates. The properties of **126** may be determined by the low probability of intramolecular dative interactions between phosphorus and boron atoms. The nearly planar conformation of the ring, the presence of repulsive interactions between the lone electron pairs of oxygen and phosphorus, and the phosphino group being in a pseudo-axial orientation do not favor the transannular intramolecular interaction of the heteroatoms. The same reasons exclude the trans-annular $\text{P}\text{---B}$ interaction in the 1,3,2,5-dioxaboraphosphorinanes. One may also exclude the $n\text{---}\sigma^*$ stabilizing interaction of the phosphorus lone electron pair and the antibonding σ^* ($\text{C}\text{---O}$) orbital. Such interaction in 1,3,2,5-dioxaboraphosphorinane causes no significant shift of the phosphorus signal in the NMR spectrum (61USP2984683; 83MI1). At the same time, neither a pseudo-equatorial nor a pseudo-axial orientation of the phosphino group excludes intermolecular $\text{P}\text{---B}$ interactions with the formation of dimers or oligomers.

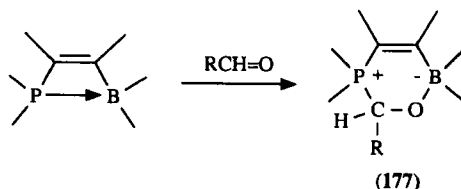
V. Heterocyclic Compounds with $\text{P}\text{---C}\text{=C}\text{---B}$ Fragments

When varying the fragment separating the phosphorus and boron atoms, one can observe changes in the types of interaction between these two atoms. In the $\text{P}\text{---C}\text{---O}\text{---B}$ system of boryloxyalkylphosphines there is a through-bond intermolecular interaction. With borylphosphinoethenes the case is different.

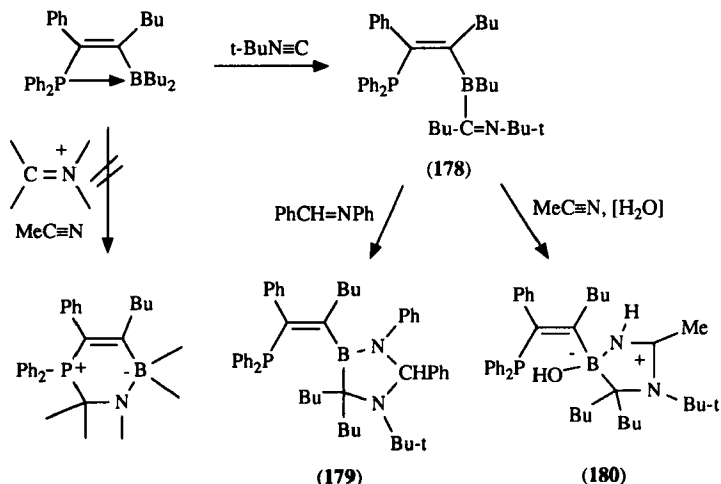




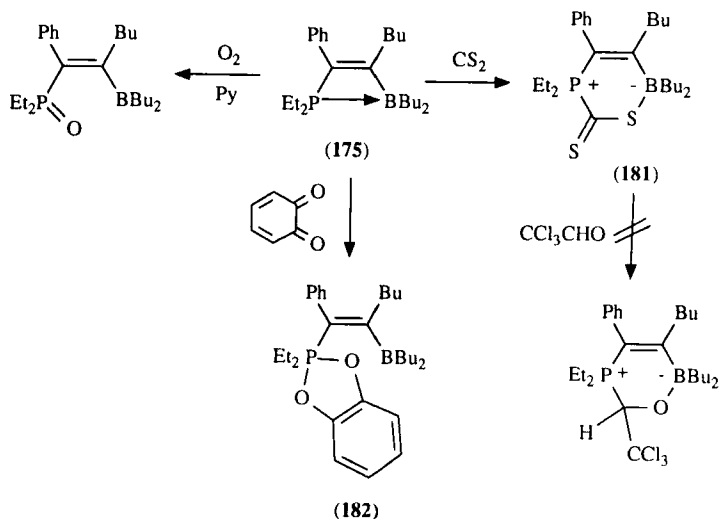
the dipole moments, and X-ray and mass spectral data all prove the existence of the P→B dative bond. An electron density transfer 0,3 e was calculated from a comparison of experimental and theoretical dipole moments. Yet this bond is not strong enough to influence reactivity. Thus, (175), (176) interacts with aldehydes, forming 3,4,6-borataoxaphosphoniacyclohexenes (177) [Eq. (133)]. This reaction is similar to the one where 1,3,2,5-dioxaborataphosphoniarinanes are formed by the addition of aldehydes to the compounds containing the P(III)—C—O—B(III) fragment.



Borylphosphinoethene derivatives were synthesized by varying the dipolar reagents. Thus, (176) appeared to interact with *t*-butyl isocyanide as trialkylborane, yielding unstable iminoborane 178. The latter forms 2-phosphinoethenyl-1-bora-2,4-diazacyclopentane (179) with benzalaniline and 1-hydroxy-1-phosphinoethyl-1-borata-2-ammonia-4-azacyclopentane-2 (180) with acetonitrile [Eq. (134)] (90IZV2147).

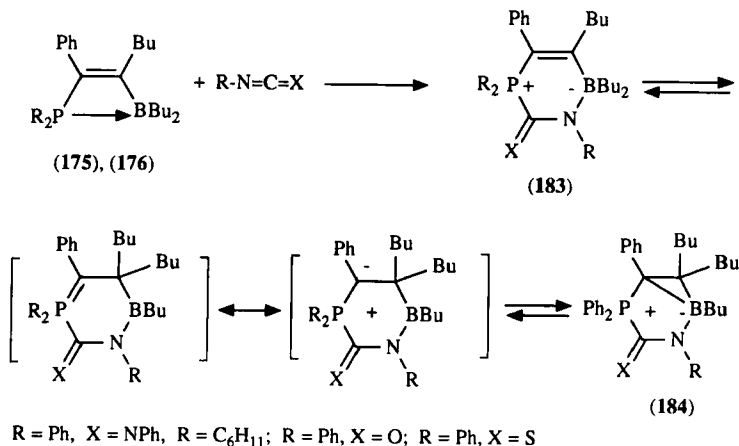


Initially borylphosphinoethene (**176**) is inert to compounds containing multiple bonds such as $C=N$, $C=N$, and $C=S$. However, substitution of phenyl by ethyl changes the reactivity. For example, 1-butyl-1-dibutylboryl-2-diethylphosphine-2-phenylethene (**175**) reacts with chloral, yielding betaine. Moreover, **175** is more easily oxidized and, in contrast to (**176**), reacts with carbon disulfide, yielding the brightly colored adduct **181** [Eq. (135)] (90IZV2613). The ^{31}P chemical shift of this compound, the large dipole moment, and the IR spectra of solutions and crystals indicate that **181** is a monomeric betaine that can possess both cyclic and open-chain structures. X-ray data indicate a tetrahedral configuration of boron and phosphorus and a short distance between the latter and one of the S atoms. Thus, it follows from the above that **181** exists mainly in a betaine cyclic form.



The disulfide fragment separating phosphorus and boron atoms was not replaced in **181** by chloral even after refluxing in benzene, evidence for high betaine stability. In methylene chloride, **175** reacts with 1,2-naphthoquinone, yielding phosphorane **182** [Eq. (135)]. This result is surprising, as one could have expected the formation of a betaine structure.

Recently borylphosphinoethenes **175** and **176** were shown to undergo $[4+2]$ -cycloaddition reactions with heterocumulenes, resulting in the formation of oxo-, thio-, or imino-1-aza-5-phosphonia-2-boratacyclohexa-3-enes **183** [Eq. (136)]. These monocyclic betaines undergo an anionotropic rearrangement, forming bicyclic betaines and 2-aza-4-phosphonia-1-boratabicyclo-[3,1,0]hexanes (**184**). This rearrangement is reversible and the reverse process is the migration of a butyl anion from an sp^3 -hybridized

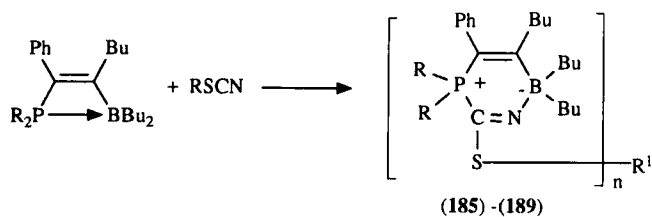


carbon atom to an sp^3 boron atom (91IZV1209, 91IZV2393; 92BAU2099, 92IZV335).

The structure of compounds **183** and **184** was established by X-ray investigation. Equilibrium processes were studied by NMR and IR spectroscopy.

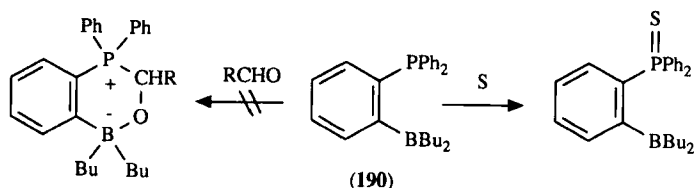
The interaction of 1,2-borylphosphinoethene with alkylthiocyanates gives compounds possessing the structure of 6-alkylthio-1,5,2-azaphosphoniaboratacyclohexa-3,6-dienes (**185**)–(**189**) [Eq. (137)] (92IZV-1638).

As shown by an X-ray study (92IZV1638), the ring in **186** was planar within 0,010(2) Å. Comparing chemical properties of *o*-borylphenylphos-



R = Et, R¹ = Me, n = 1 (**185**); R¹ = Ph, R = Me, n = 1 (**186**)

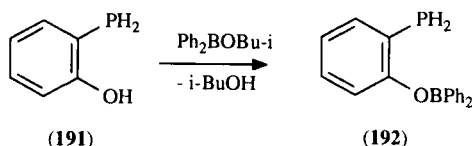
R = Ph, R¹ = Bz, n = 1 (**187**); R¹ = Ph, R = -CH₂-, n = 2 (**189**)



phines (**190**) (911ZV2397) and borylphosphinoethenes, both containing the $P-C\equiv C-B$ fragment, one should note their different reactivity to aldehydes [Eq. (138)]. Whereas the latter easily undergo $[4+2]$ -cycloaddition reactions, *o*-borylphenylphosphine does not react with aldehydes even on prolonged refluxing in benzene.

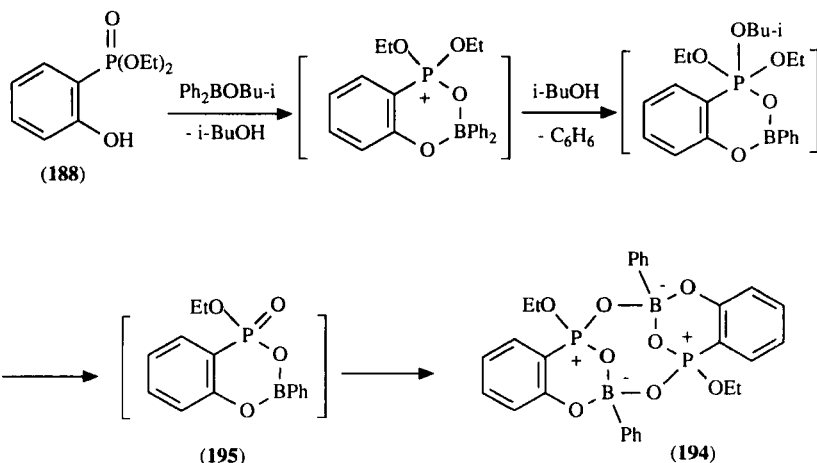
VI. Miscellaneous P,B-Containing Heterocyclic Compounds

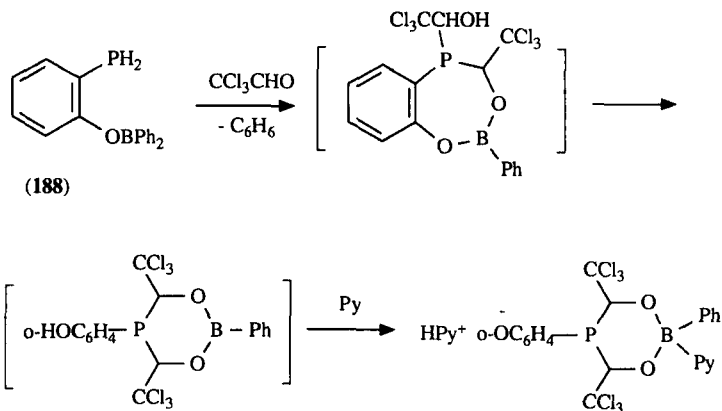
Compounds with $P-C\equiv C-O-B$ fragments: Borylation of *o*-oxyphenylphosphine (**191**), giving rise to *o*-diphenylboryloxypheylene-phosphine (**192**), proceeds only under severe conditions [Eq. (139)] (911ZV477).



Reaction with *o*-oxyphenylphosphonate (**193**) also proceeds at high temperatures, but in this case a dimer (**194**) of the corresponding 1,3,2,4-dioxaboraphosphorinane (**195**) is obtained. Its structure was confirmed by an X-ray [Eq. (140)] (911ZV477). Reaction is likely to proceed with the participation of isobutyl alcohol, formed at the first stage.

Some chemical properties of boryloxypheylene-phosphines (**192**) have been studied [Eq. (141)]. In Balueva *et al.* (911ZV2397) the intramolecular *trans*-esterification of phenylboric acid, a phenyl ester with α -





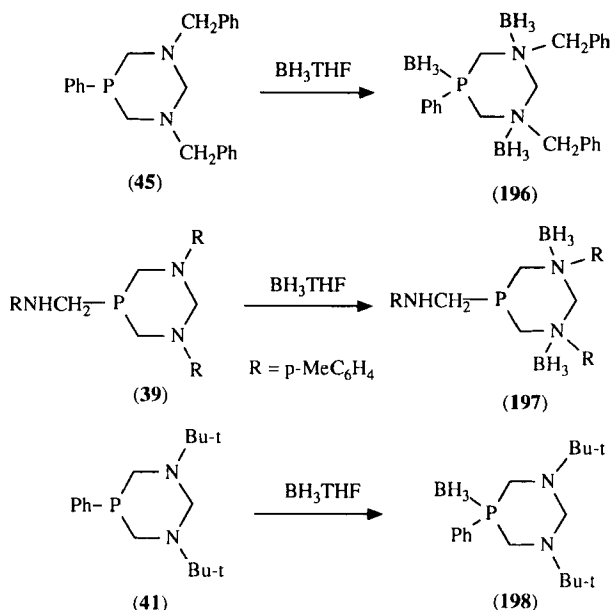
hydroxyalkylphosphine is produced as product. The above property may indicate that compounds with the $\text{P}-\text{C}-\text{O}-\text{B}$ fragment are more stable than molecules, containing the $\text{P}-\text{C}=\text{C}-\text{O}-\text{B}$ unit, due to through-bond phosphorus-boron stabilizing interactions.

Compounds with $\text{P}-\text{C}-\text{N}-\text{B}$ fragments: Compounds containing the $\text{P}-\text{C}-\text{N}-\text{B}$ fragment can be obtained in the borylation reactions of functionally substituted phosphines with boranes (88IZV2190; 89IZV1375). As a rule, the first stage is characterized by the formation of complexes in all cases.

For example, 1,3,5-diazaphosphorinanes (39), (41), (45) interact with borane to give white crystalline substances (196)–(198) [Eq. (142)], which were assigned the structure of the corresponding complexes in accordance with an NMR and IR study.

A comparison of the structures of products and initial 1,3,5-diazaphosphorinane reactants reveals a correlation between the number of added borane molecules and the predominant conformation of the initial compounds. 1,3-Dibenzyl-5-phenyl-1,3,5-diazaphosphorinane (45) adopts a chair conformation. The substituents at the phosphorus atom and at one of the nitrogen atoms are equatorial, and another nitrogen possesses an axial substituent. In other 1,3,5-diazaphosphorinanes, all the substituents are equatorial. The number of borane molecules added is likely to be determined by the same factors as their conformational stability. There is steric hindrance when the three BH_3 groups are axial.

Bis(α -aminomethyl)phosphines having a mobile hydrogen atom could be expected to undergo a borylation reaction with borane, hydrogen being evolved. In fact, bis(*N*-phenylaminomethyl)-phenylphosphine (199) and its sulfide (200) appeared to interact with borane under mild conditions, yielding a new type of phosphorus-boron-containing heterocycle—2-

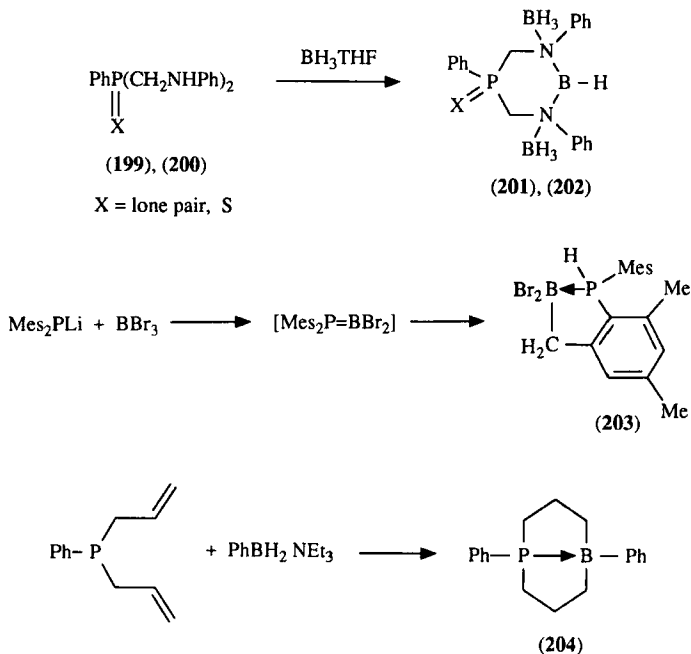


hydroxy-1,3,2,5-diazaboraphosphorinanes (**201**) and its sulfide (**202**) [Eq. (143)] (88IZV2190).

The above compounds contain both cyclic and acyclic P—C—N—B fragments. Complexes formed at the first stage of the reaction undergo a series of successive transformations depending on the electronic and structural characteristics of the substituents and the presence of a mobile hydrogen at heteroatoms.

Several studies are known describing P,B-containing heterocycles with a chain of three or more carbon atoms separating phosphorus and boron. In this case a trans-annular donor–acceptor interaction between phosphorus and boron is observed, resulting in the formation of a P—B intramolecular bond. In this respect the study of Karsch and co-workers is of special interest (89CC373). They made an attempt to obtain dimesitylphosphineborane from lithium dimesitylphosphide and tribromoborane. However, a new type of heterocycle (**203**) was synthesized. Reaction was accompanied by a 1,3-migration of a hydride ion [Eq. (144)].

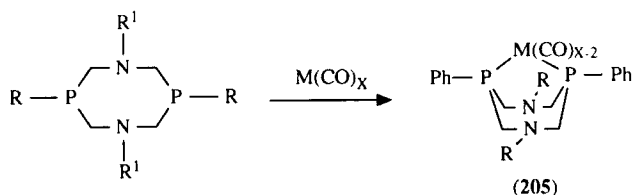
The formation of a strong intramolecular dative P—B bond in the hydroborylation reaction of diallylphenylphosphine with triethylaminophenylborane results in a bicyclic product, 1-borata-5-phosphoniabicyclo[3,3,0]octane (**204**) [Eq. (145)] (64JA5045). The presence of the dative bond in this compound is indicated by an NMR study and by its stability to hydrolysis and oxidation.



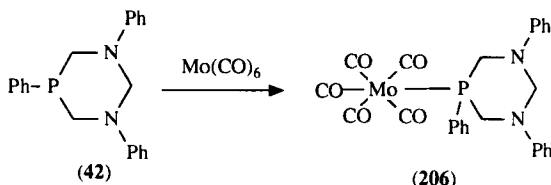
VII. Metal Complexes Containing P-Heterocyclic Ligands

Functionally substituted phosphines play an important role as ligands in a great variety of phosphorus coordination compounds. They have some interesting features that distinguish them from other phosphine ligands, namely (a) the presence of other heteroatoms bearing lone electron pairs in addition to phosphorus; (b) the presence of functional groups able to form bonds with a metal with the participation of its valence electrons; (c) the presence of heteroatoms with a vacant orbital such as boron; and (d) high lability of the P—C bond and stereoisomerism, typical of cyclic phosphines. Cyclic oxyalkylphosphines and aminomethylphosphines, unlike their acyclic analogues, are not studied as ligands and chelates in coordination compounds. In heterocycles possessing several donor centers, the question about the competition to participate in coordination bonds is yet to be solved. The reverse dative effect appears in the case of acceptor centers such as a tricoordinated boron atom.

Complexes of diazadiphosphacyclooctanes with molybdenum carbonyl have been obtained [Eq. (146)] (80TL1409, 80TL1845; 81TL1105). In this case heterocycles play the role of a chelate.



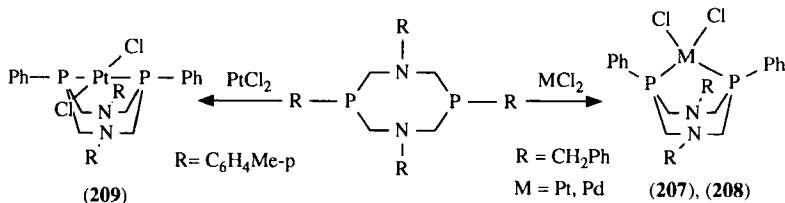
In order to exclude chelating effects, 1,3,5-diazaphosphorinanes were used in Karasik *et al.* (92IZV201). In this case the substitution of only one carbonyl group took place [Eq. (147)]. But it should be noted that reaction conditions were different.

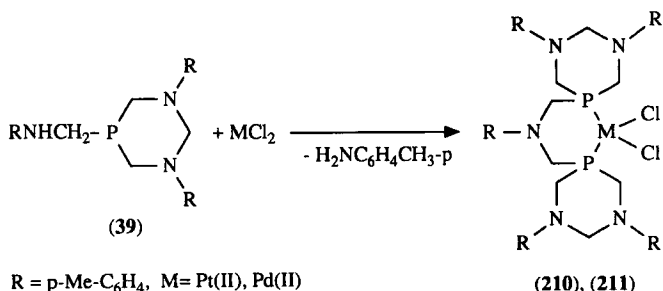


In a study of diazadiphosphacyclooctane complexes with Pt(II) and Pd(II), the dependence of the configuration of the central atoms on substituents at nitrogen was revealed, although the metal is coordinated with phosphorus. Thus, *cis* complexes (207), (208) are obtained for PtCl₂ and PdCl₂, when R = CH₂Ph. And *trans* complex (209) was formed for PtCl₂ when benzyl substituents were replaced by aryl groups [Eq. (148)] (90IZV2452; 92IZV335). For compound (209) the formation of a binuclear complex with a *trans* configuration of metal atoms is also possible.

The structure of the complexes in solution and in crystals was established using spectral methods and by comparison with the data for initial ligands. This approach made it possible to determine the structure of new ligands formed in the reaction by complexation.

Compound (39) reacts with Pt(II) and Pd(II) chlorides at room temperature in CH₃CN and CHCl₃, respectively. But in both cases coordination of two ligands with the metal atom was accompanied by nucleophilic substitution at the exocyclic carbon atom. Complexes (210) and (211) having a novel chelate bicyclic ligand with Pt(II) and Pd(II) have been formed in the course of template processes [Eq. (149)] (92IZV335, 92MI1).





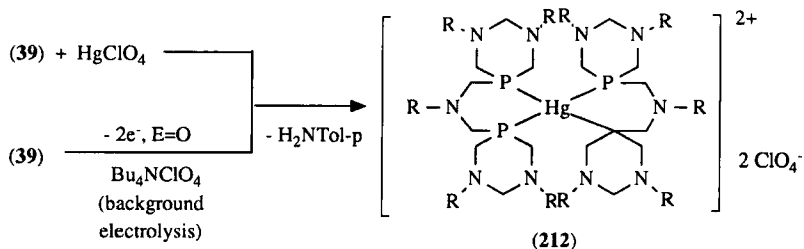
The ^{31}P and ^1H study revealed the configuration of the central atom and the conformation of the cyclic ligand fragments, as well as the orientation of M-P bonds. The Pt-P bond is equatorial in the 1,3,5-diazaphosphorinane cycle.

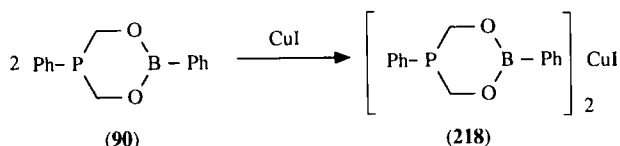
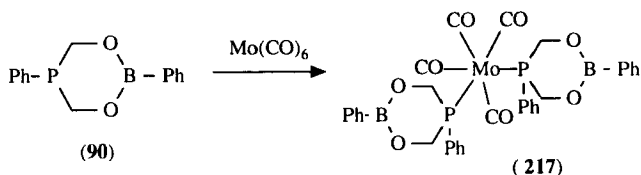
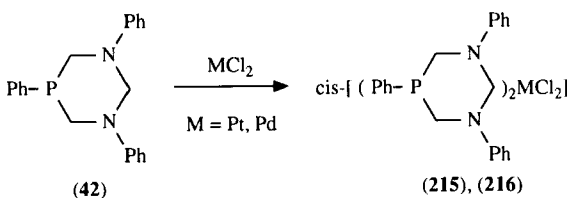
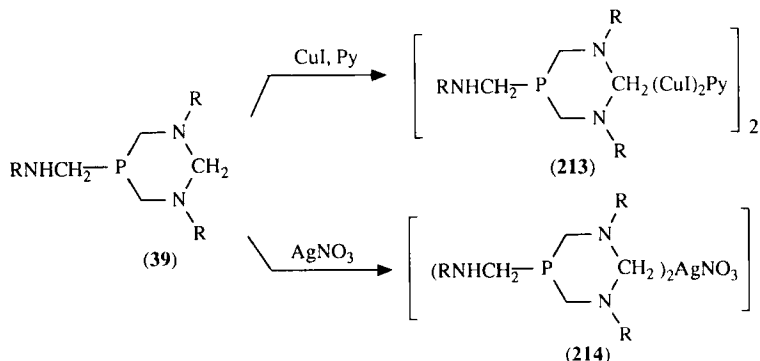
With a metal ion having four coordination centers, binding of four molecules (39) can occur. The reaction of four molecules of (39) with Hg(II) perchlorate in CH_3CN produced complex (212) with a high yield [Eq. (150)]. Electrochemical oxidation of some phosphines on a mercury anode has been shown to lead to their complexes with Hg(II) . Following this method, complex 212 was synthesized in high yield (92MI1). The M-P bonds were shown to be in an equatorial position.

Notably, dimerization of ligands was not observed when the complexes with Cu(I) salts and AgNO_3 were formed. Metal atoms were expected to coordinate nitrogen [Eq. (151)].

1,3,5-Diazaphosphorinane (42) gives *cis* complexes (215), (216) with PdCl_2 and a metal coordinating phosphorus atom [Eq. (152)] (91IZV209, 92IZV335).

Of great interest as ligands are 1,3,2,5-dioxaboraphosphorinanes. They can behave as typical phosphine ligands, giving complexes with molybdenum carbonyl (217) [Eq. (153)] (92IZV201). An NMR and IR study showed this complex (217) to have a *cis* structure. 1,3,2,5-Dioxaboraphosphorinane (90) forms coordination compounds with a 2:1 ratio with copper iodide, the ratio being independent of the composition of reagents [Eq. (154)] (91IZV358, 91IZV906). Attempts were made to determine the center

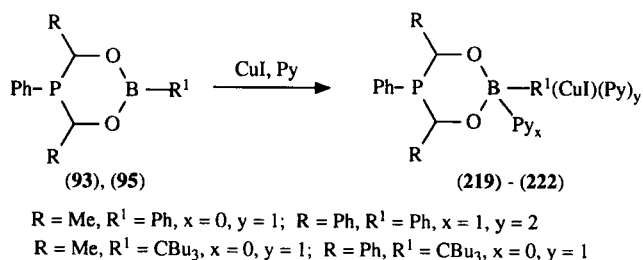




of metal coordination in the heterocycle and the conformation of dioxaboraphosphorinane fragments.

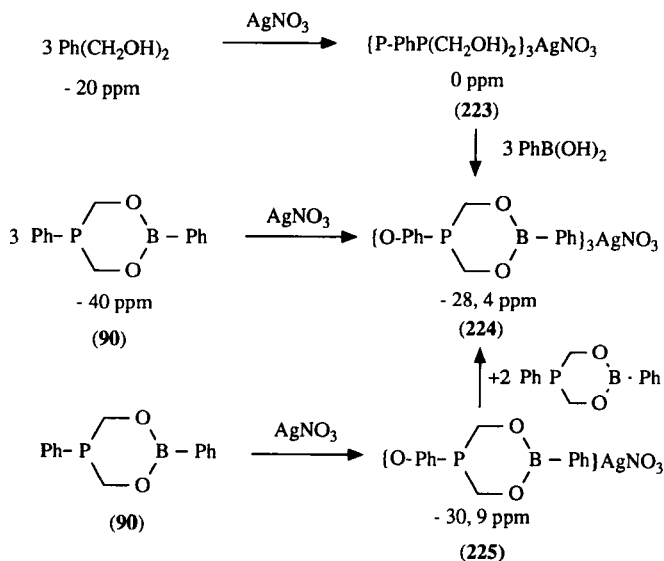
The presence of substituents and the use of pyridine as solvent changes the ratio of ligands. In the case of donor or weak acceptor substituents the formation of complexes with Cu(I) takes place, stable crystalline compounds being obtained only in the presence of pyridine. In all the cases copper forms complexes with one phosphorus ligand but the number of pyridine molecules varies from 1 to 3 [Eq. (155)].

Complexes with silver nitrate are also obtained, the number of ligands depending on the ratio of reagents [Eq. (156)]. Notably, the ^{31}P chemical shift changes from -20 to 0 ppm on addition of silver nitrate to bis(oxy-methyl)phenylphosphine. This change probably results from the coordina-

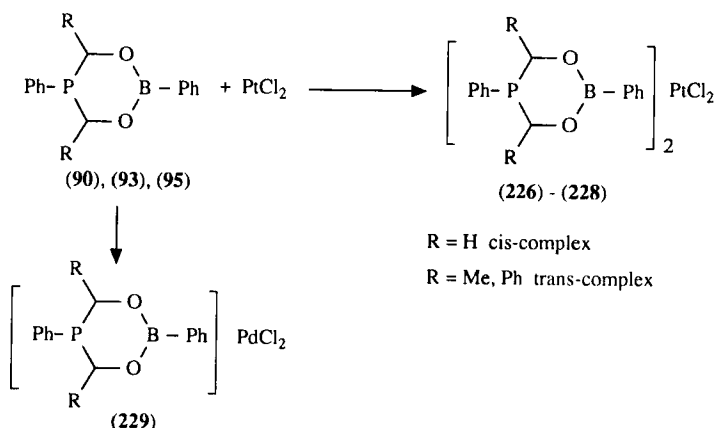


tion of the phosphorus atom. The resultant complex (223) reacts with phenylboric acid giving the complex 224 with the chemical shift close to that of dioxaboraphosphorinane (40). The metal atom was expected to migrate in the process of cyclization. Such change of the coordination may be determined by a decreasing phosphorus nucleophilicity in dioxaboraphosphorinane.

1,3,2,5-Dioxaboraphosphorinanes have three nucleophilic centers (phosphorus and two oxygen atoms). The effective negative charge on oxygen is increased due to the low electronegativity of the boron atom and phosphorus nucleophilicity is decreased due to the n-o* interaction of its lone electron pair and the C—O bond. Thus the charge and orbital effects in complexation reactions compete with each other. In Karasik *et al.* (91IZV2309) complexes of 4,6-disubstituted 1,3,2,5-dioxaboraphosphorinanes with Pt(II) and Pd(II) salts (226)–(229) were obtained. The configuration of the central ion was found to depend on



substituents in the heterocycle. *cis* complex **226** was obtained for $R = H$, whereas $R = Me, Ph$ a *trans* configuration was realized in complexes **227, 228**. The NMR study of solutions showed the ligand of complex **226** to adopt an assymmetrical twist conformation, which is likely to be stabilized by an additional interaction between the ligand and the central ion. Compound **90** forms complex **229** with a 1 : 1 ratio of metal to ligand, even in the presence of excess of the latter [Eq. (157)].



VIII. Utilitarian Aspects

Utilitarian aspects of these heterocyclic phosphines are much less studied than those of their acyclic analogues. Thus, the fire resistivity of materials increases on treatment with aminomethylphosphines. With this aim, polymers generated by the interaction of phosphine with formaldehyde and amine can be used (62BRP919267). The same effect is observed for 1,3,5-triaza-7-phosphaadamantane (74USP374584) and 3,7-dicyano-3,5,7-triaza-1-phosphabicyclo[3,3,1]-nonane and its derivatives (74-USP391189).

Functionally substituted phosphines and their derivatives are used as fungicides and herbicides. The results of investigations on antiviral activity and toxicity of a series of compounds belonging to oxymethyl and aminomethyl phosphine derivatives, including those with the $P-C-O-B$ fragment, are reported in Molodyuh *et al.* (83MI2; 85MI1; 87MI2). The dependence of physiological activity on the nature of the heterocycle, phosphorus atom coordination, and chemical properties has also been studied. The lowest activity was observed for 1,3,5-dioxaphosphorinanes and their derivatives. The replacement of an oxygen

by a nitrogen atom in six-membered heterocycles has no significant influence on activity. However, the introduction of a boron atom into a 1,3,5-dioxaphosphorinane ring results in fungicidal activity. Increased activity is observed on going from P(III) derivatives to phosphonium salts.

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Mono- and Diazaquinones¹

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¹ Dedicated to Dr. Alfred Bader on the occasion of his 70th birthday.

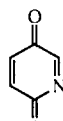
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I. Introduction

Quinones constitute an important class of naturally occurring compounds that are involved in many biochemical processes. Some of them, which are usually called heterocyclic quinones, contain a heterocyclic ring fused onto the quinonoid moiety.² In addition, some quinones also have important synthetic and/or industrial applications. Therefore, it is not surprising that numerous reviews on both quinones and heterocyclic quinones are available in the literature. Two volumes of the Houben–Weyl series and two volumes of *The Chemistry of Quinonoid Compounds* edited by Patai in 1974 (74MI1) and their updated version edited by Patai and Rapport in 1988 (88MI1) are perhaps the most comprehensive. Recent specialized reviews on both quinones (91T8043) and heterocyclic quinones (89AHC37) are also available. Surprisingly, the only review dealing with quinones that contain a nitrogen atom directly within the quinonoid ring (azaquinones) is a review on diazaquinones (78H1771). The scarcity of reviews calls for a comprehensive summary of this exciting area of heterocyclic chemistry. This paper describes monoazaquinone and diazaquinone compounds and also includes quinonoid structures containing one or two bridgehead nitrogen atoms. What follows is a brief treatment of the most investigated structures of this class.

II. Monoazabenzoquinones

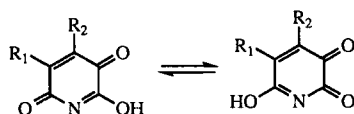
Formally two aza analogs of *o*-benzoquinone (**1,2**) and one aza analog of *p*-benzoquinone (**3**) are possible.

**1****2****3**

² The term heterocyclic quinones is used in the literature for quinones having a heterocyclic ring fused directly onto the quinone moiety. The term azaquinones is usually restricted to compounds having nitrogen atoms as members of the quinonoid rings. Throughout the text terms heterocyclic quinones and azaquinones are used in this way.

A. SYNTHESIS AND HISTORICAL BACKGROUND

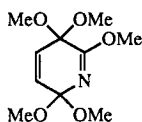
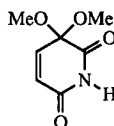
This class of compounds was first introduced into the literature by Kudernatsch, who reported that oxidation of 2,3- and 2,5-pyridinediols provided compounds **1** and **3**, respectively (1897M613). Boyer and Krueger later tried to prepare **1** and **3** by oxidation of 3-amino- and 5-amino-2-pyridinol, respectively, under strongly acidic conditions (57JA3552). They reported that hydroxylation occurred during the oxidation and that both starting aminopyridinols provided the same hydroxyazabenzquinone **4a**. Formation of **4b** from the corresponding methyl derivatives of the starting aminopyridinols was also reported. They also repeated the Kudernatsch's experiment and obtained the same product as from the aminopyridinols. Moore and Marasica synthesized compound **4c** by hydrolysis of 4-methyl-6-nitroso-3-phenylpyridinediol (59JA6049). In connection with their studies on anodic oxidation, Weinberg and Brown isolated azaquinone ketal **5** from the reaction mixture after anodic methoxylation of 2,6-dimethoxy-pyridine (66JOC4054). They found that hydrolysis of **5** with dilute acetic acid provided acetal **6**, which, after hydrolysis with hydrochloric acid, provided the same product that was isolated and identified as **4a** by Boyer and Kruger.



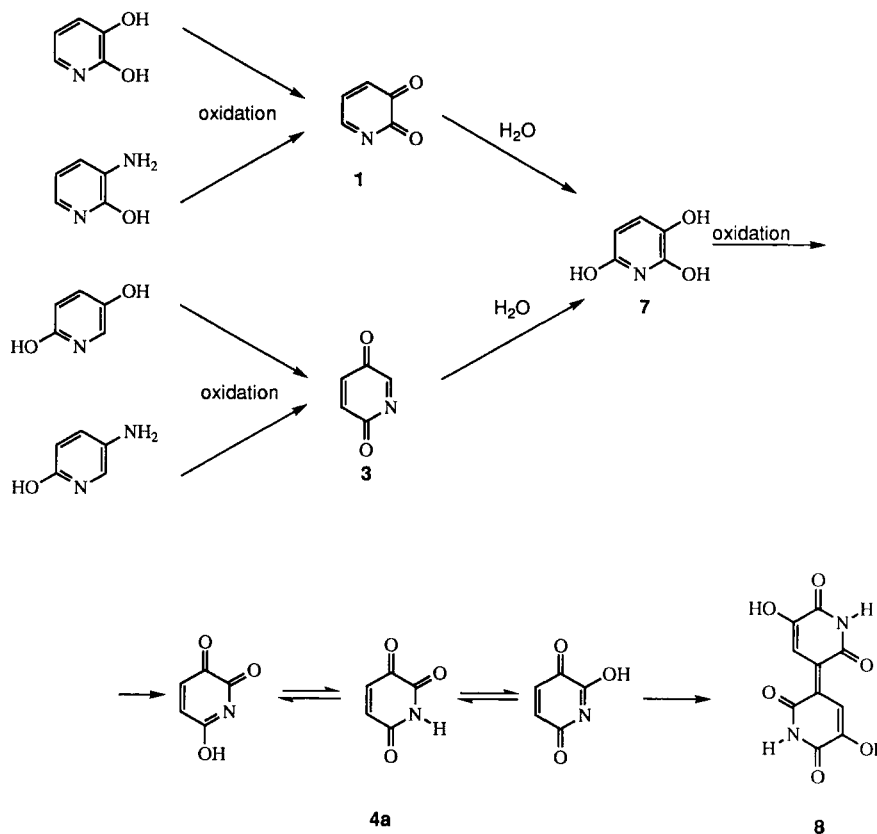
4a $R_1 = R_2 = H$

4b $R_1 = Me, R_2 = H$

4c $R_1 = Ph, R_2 = Me$

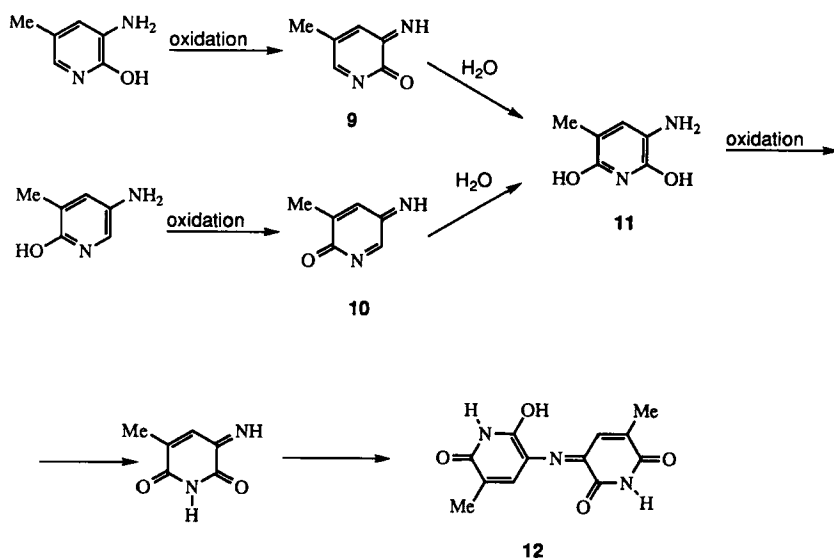
**5****6**

Knackmuss investigated indigoidine bacterial secondary metabolites and during these studies found inconsistency in the literature data on the azaquinones. Therefore he reinvestigated this field and discovered several important facts. He found that oxidation of both corresponding pyridinediols and aminopyridinols gives neither azaquinones **1** and **3** nor compound **4a** but that the reaction product was rather dimeric structure **8** (Scheme



SCHEME 1

1). The azaquinones **1** or **3** are primarily formed by oxidation but the $C=N$ bond of these compounds undergoes hydration to 2,3,6-trihydroxypyridine **7**, which is further oxidized to **4a**. Its ketoform, which is 2,3,6-trioxo-1,2,3,6-tetrahydropyridine, then dimerizes into **8** (65CB2139). This type of dimerization cannot occur with compounds having a substituent at the position 5. Since properties of the compound isolated from oxidation of the 3-amino-5-methyl-2-pyridinol and 5-amino-3-methyl-2-pyridinol did not correspond to the structure of **4b**, Knackmuss also reinvestigated the oxidation of these substrates and identified dimeric structure **12** as the product (68CB1148; 68CB2679). The proposed mechanism, which is depicted in Scheme 2, again involves oxidation of the starting compounds followed by hydration of the reactive $C=N$ bond in the intermediate imine

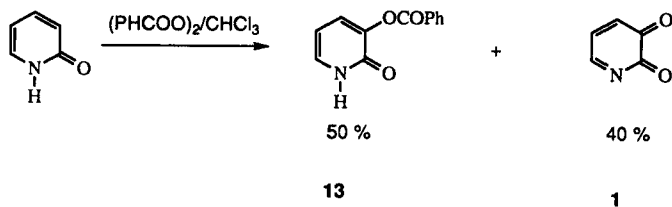


SCHEME 2

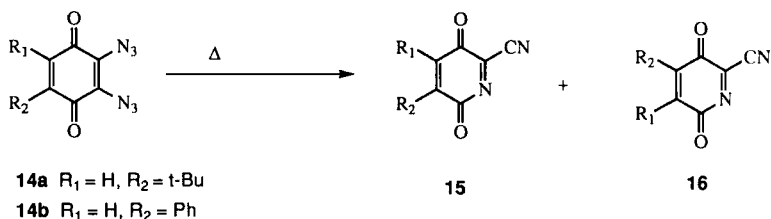
structures **9** and **10**. The hydration in both cases yields **11**, which is dimerized to the final product.

From this perspective one realizes that most previous literature data were greatly impacted by the Knackmuss reinvestigation, the results of which are summarized in a review [73AG(E)139]. The only correct structure of an azaquinone previously reported appears to be that of compound **4c**, which could not undergo dimerization due to its substitution pattern. A more recent report claims that oxidation of 2-pyridone with dibenzoyl peroxide in chloroform gave 50% of 3-benzyloxy-2-pyridone **13** and 40% of azaquinone **1** (Scheme 3) [85IJC(B)972].

A quite different approach was utilized for the synthesis of 2-aza-3-cyano-1,4-quinones (Scheme 4). Thermal rearrangement of 2,3-bisazido-



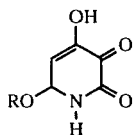
SCHEME 3



SCHEME 4

1,4-quinones provided the corresponding 2-aza-3-cyano-1,4-quinones in low to moderate yields; e.g., 1:1 mixture of **15a** and **16a** was obtained in 55% isolated yield from thermolysis of unsymmetrically substituted diazidoquinone **14a**. Analogous phenyl derivative **14b** afforded the corresponding products, albeit in lower yield.

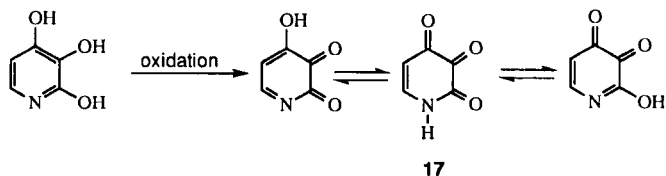
In contrast to the azaquinones **1** and **3**, there is no literature report on the isomeric azaquinone **2**. Reported hydroxy azaquinone **17** obtained by oxidation of 2,3,4-pyridinetriol can be considered to be its 2,3-dioxo-4-hydroxy tautomer (Scheme 5) (1883JPR257). In addition, this compound was identified only as its solvate with the alcohol of crystallization, which suggests the possibility of structure **18** instead [73AG(E)139].



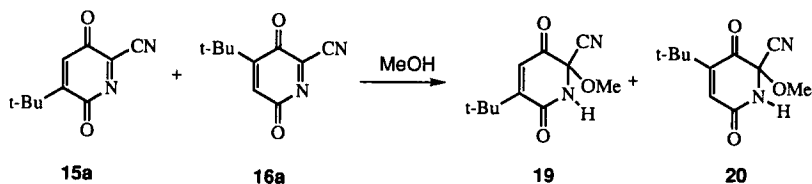
18a $R = \text{Me}$
18b $R = \text{Et}$

B. STABILITY AND REACTIONS

As described earlier, the $\text{C}=\text{N}$ double bond of the azaquinone structures is readily hydrated to provide the corresponding hydroxy derivatives, a principal step involved in their dimerization. Generally the chemis-



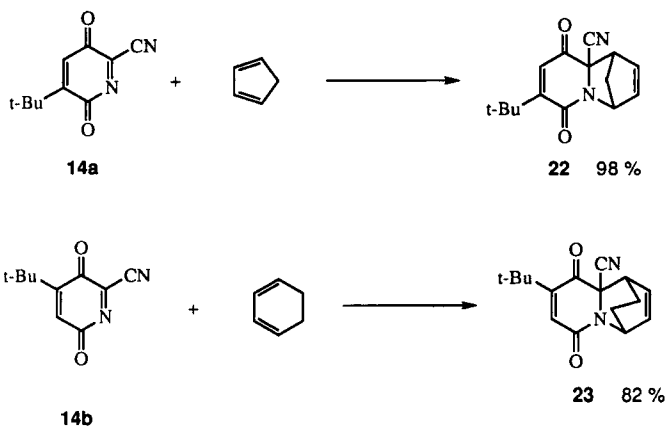
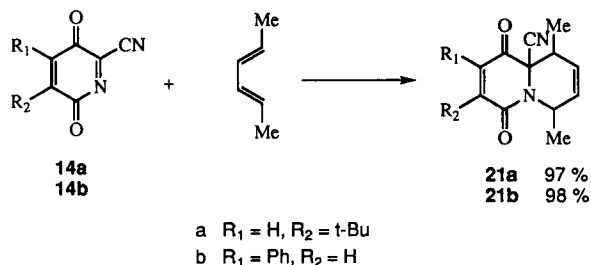
SCHEME 5



SCHEME 6

try of azaquinones is centered on the electron-deficient imine double bond. For example, a mixture of **15a** and **16a** was treated with methanol and yielded a mixture of the corresponding methanol adducts **19** and **20**, which were isolated and characterized (Scheme 6).

As expected, the azaquinone C=N double bond is strongly dienophilic. This was demonstrated by reactions with several 1,3-butadienes, cyclopentadiene, and cyclohexadiene (Scheme 7). These reactions, carried out



SCHEME 7

at 25°C, were complete within seconds and the cycloadducts **21a**, **21b**, **22**, and **23** were isolated in generally high yields (75JA6181).

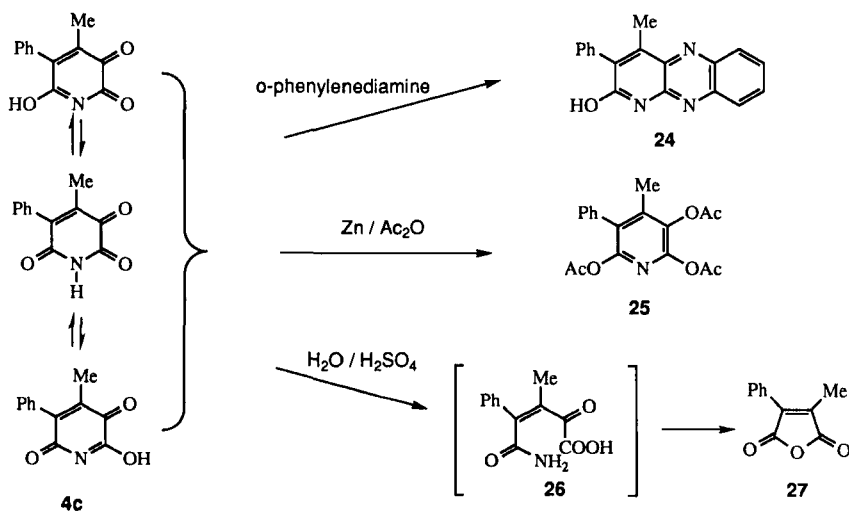
The corresponding hydroxyazaquinones appear to exist mainly in their trioxo tautomeric forms. The only structure of this type, which has been described in subsequent trapping reactions (Scheme 8), is compound **4c** (59JA6049). This compound when treated with *o*-phenylenediamine in acetic acid provided pyrido[2,3-*b*]quinoxaline **24**. Reduction of **4c** with zinc in acetic anhydride provided triacetoxypyridine derivative **25**. Acidic hydrolysis of the azaquinone provided maleic anhydride derivative **27**, probably via intermediate **26**.

C. SPECTROSCOPIC PROPERTIES

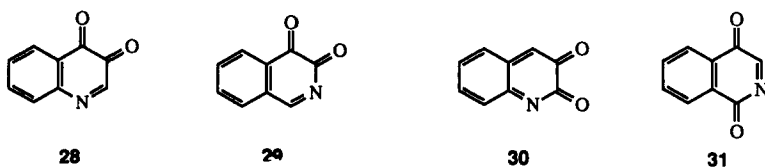
Azaquinoid structures have been detected by ESR along with several radical species formed by the *in situ* radiolysis of 3- and 5-hydroxy-2-pyridones in aqueous solutions (76T261; 79JPC2407; 90T2891).

III. Monoazanaphthoquinones

There are four possible monoazanaphthoquinones, two of which are derived from 1,2-naphthoquinone (**28** and **29**), one derived from 2,3-naphthoquinone (**30**) and one derived from 1,4-naphthoquinone (**31**).



SCHEME 8

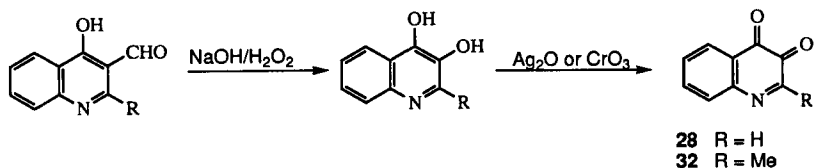


A. SYNTHESIS

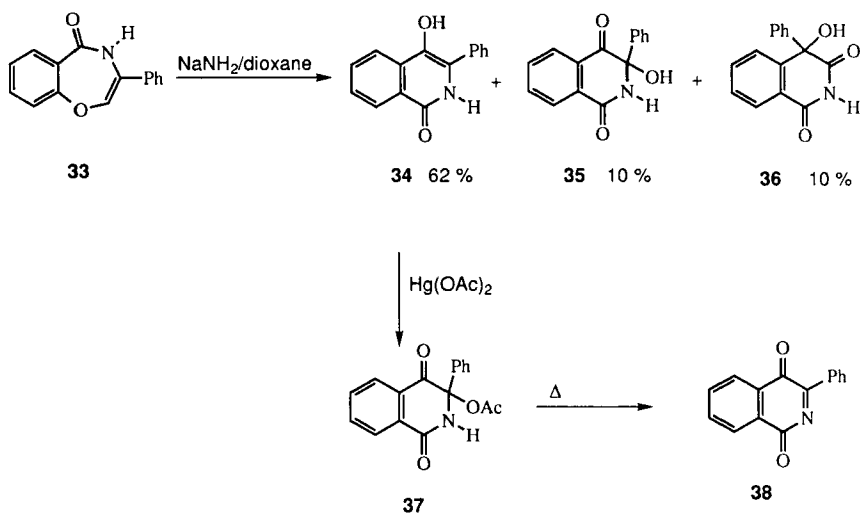
The reactive nature of monoazabenzophenones suggested that the anelation of a benzene ring in such congeners could increase their stability. Indeed, the first known monoazaphthoquinone **28** was isolated by Passerini *et al.* as early as 1931 (31G959). They isolated *N,N'*-diphenylurea from a reaction mixture of phenyl isonitrile and nitrosobenzene, and the mother liquor on acidic treatment afforded **28**. Later Morgan *et al.* prepared the same compound as well as its methyl derivative **32** by oxidation of their corresponding diols with silver oxide and/or chromium trioxide (Scheme 9) (63JOC260).

The best studied derivative of monoazaquinone **31** is its phenyl derivative **38**. It was first prepared by Schenker, who found that readily available 1,4-benzoxazepine **33**, on treatment with sodium amide, provided a mixture of isoquinoline derivatives **34**, **35**, and **36**, in which **34** prevailed (68HCA413). Oxidation of **34** with mercuric acetate afforded a good yield of acetoxy derivative **37**. Pyrolysis of neat **37** in high vacuum or pyrolysis in refluxing toluene provided the desired azaquinone **38** in good yields (Scheme 10) (69HCA1810). Another successful approach to **38** was realized from its dihydro derivative **39** (70JHC615). Bromination in methanol provided methoxy derivative **40**. This compound is thermally stable, but on treatment with thionyl chloride and subsequent distillation furnished **38** (Scheme 11).

The thermal rearrangement of azidoquinones has been used for the synthesis of monoazaphthoquinones in analogy to that described for the synthesis of cyano monoazabenzophenones (Scheme 12). In this case, thermal decomposition of diazidonaphthoquinone **41** provided a mix-



SCHEME 9

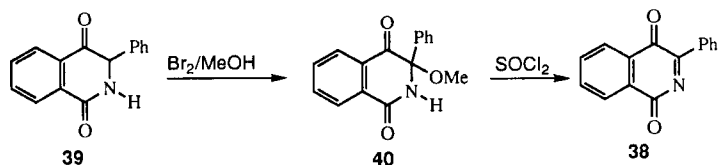


SCHEME 10

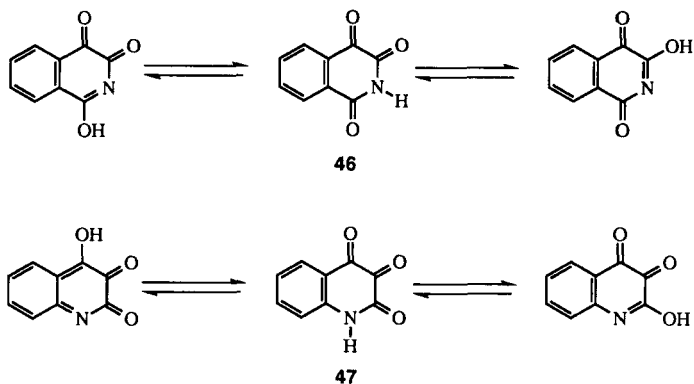
ture of **42** and **43** from which 18% of the intermediate 2-azido-2-cyano-1,3-indanedione **43** was isolated. Subsequent thermolysis of **43** provided azaquinone **44** in good yield (75JA6181). When 2-azido-2-phenyl-1,3-indanedione **45** was subjected to appropriate thermolysis conditions, **38** was obtained.

Several attempts to prepare unsubstituted azaquinone **31** have been reported, but to date, no success has been documented (69HCA1810; 70JHC615).

There are no known derivatives of **29** and **30**, except for the corresponding hydroxy derivatives, which can be present in several tautomeric forms. Therefore **46**, the hydroxy derivative of **29**, is also a hydroxy derivative of **31**, as well as the corresponding trioxo derivative. A similar argument can be made for **47**, which formally can be considered to be a hydroxy derivative of both **28** and **30**. Spectroscopic studies of similar compounds suggested that these compounds exist almost entirely in their trioxo tautomeric forms [72JCS(P1)977; 78LA283).

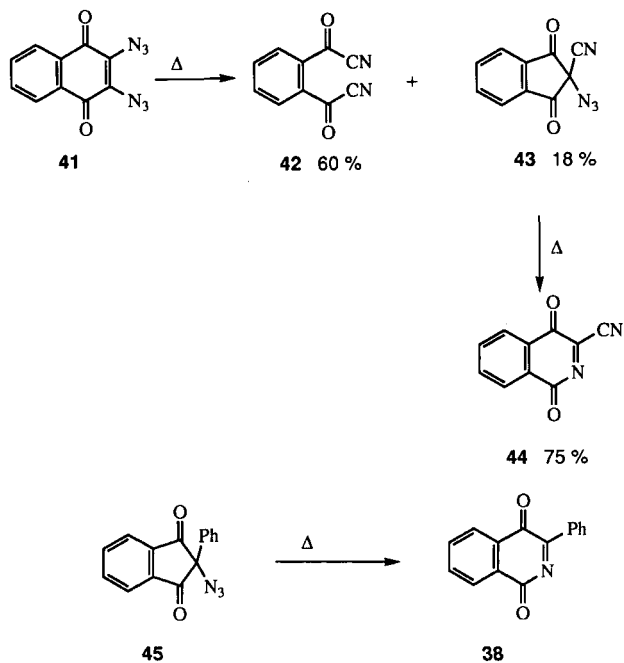


SCHEME 11



B. REACTIONS

Most reactions of the monoazanaphthoquinones are again centered around the imine $C=N$ bond. As described for monoazabenzquinones, the addition of water, alcohols, ammonia, and amines to these reactive



SCHEME 12

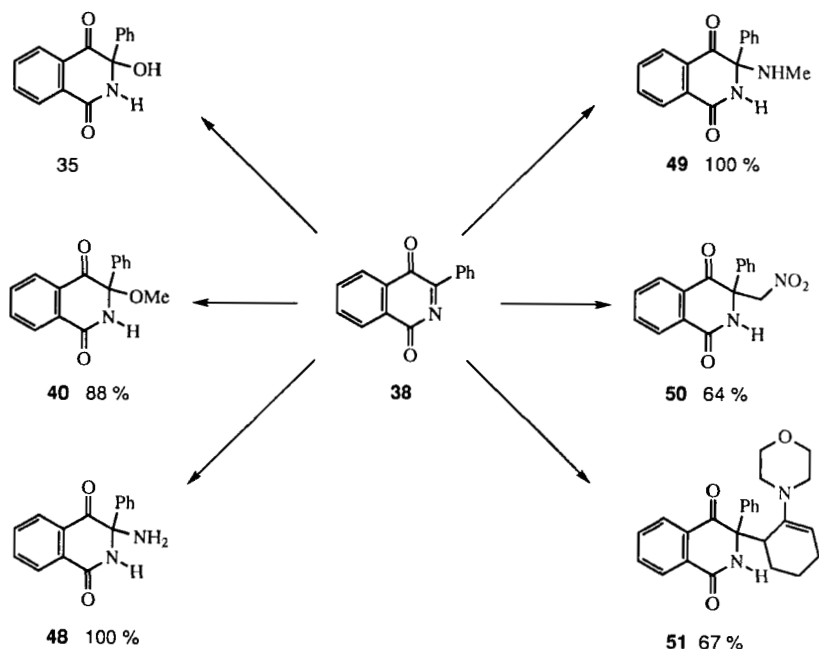
compounds is facile (69HCA1810; 70JHC615; 71TL1621). These reactions are well documented for azaquinone **38** (Scheme 13). Addition reactions of other hydrogen donors, e.g., nitromethane and 1-morpholinocyclohexene leading to **50** and **51**, respectively, have also been described (69HCA1810).

Similarly, the addition of a variety of H donors under photochemical conditions generally provided mixtures of products **52–54** (Scheme 14) (77CL1127). When xanthene was used as the hydrogen donor, structures **52** usually prevailed. On the other hand, no structures **52** were detected in the case of etheral donors such as tetrahydrofuran or 1,4-dioxane.

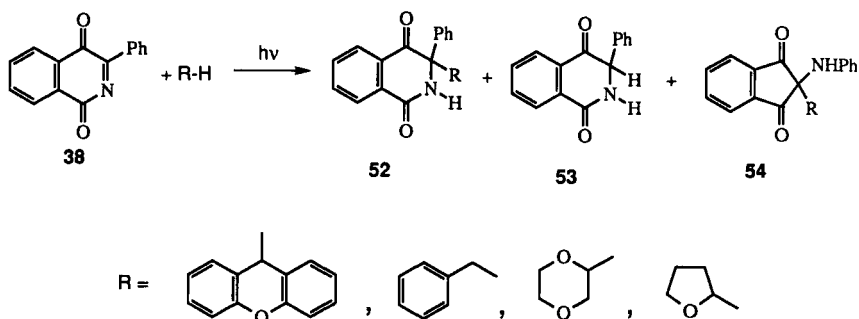
The C=N double bond is easily reduced, e.g., by refluxing with tetraline (71TL1621). As expected, the imine double bond is also very reactive toward cycloadditions. β -Lactam structure **55** is formed by 1,2-cycloaddition of *t*-butylcyanoketene to **38** (71TL1621). As with azabenzquinones, the 1,4-addition of 1,3-dienes to **38** provides the Diels–Alder products, e.g., **56** and **57**, in good yields (Scheme 15) (70JHC615; 75JA1681).

Azaquinone structures possessing two adjacent carbonyl groups provided phenazine derivatives, e.g., **58** and **59**, when reacted with *o*-phenylenediamine (Scheme 16) [63JOC260; 72JCS(P1)977].

As mentioned, structure **46** can be considered to be a hydroxy derivative

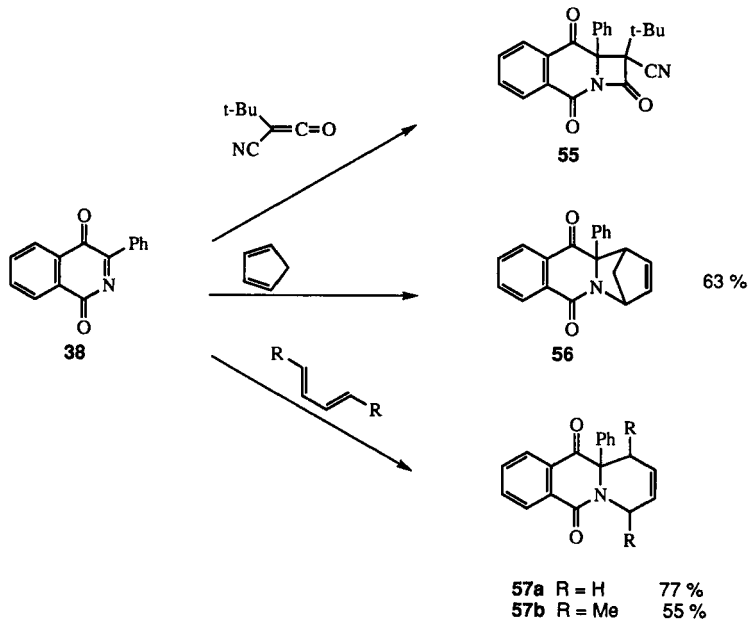


SCHEME 13

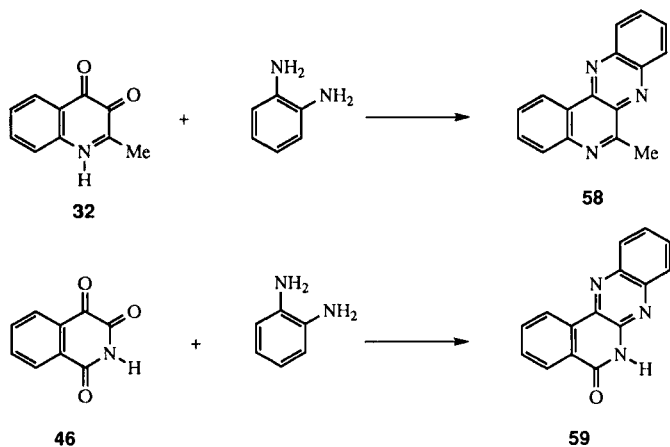


SCHEME 14

of either **29** or **31**. The compound differs from true monoazabenzquinones not only in their physico-chemical properties, but also in its reactivity. No reaction that could be interpreted as a reaction of a $C=N$ -containing tautomer has been documented. For example, reaction of **46** with ethanol in the presence of triethylamine as catalyst provided **61** via ring open intermediate **60**. A similar reaction in the presence of primary or secondary amines provided **63** (Scheme 17) (78LA283).



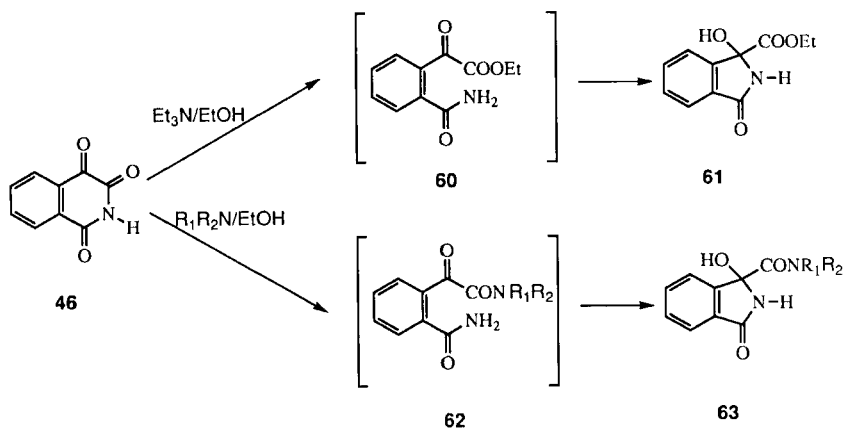
SCHEME 15



SCHEME 16

C. SPECTROSCOPIC PROPERTIES

Although azanaphthoquinones are inherently more stable than the corresponding azabenzquinones, thorough spectroscopic data of these compounds is scant. 2-Aza-3-aryl-1,4-naphthoquinones, e.g., **38**, exhibit a characteristic absorption in the region 500–540 nm, which corresponds to the lowest excited state (77CL1127). The IR spectrum of **38** contains two strong absorption bands at 1600 and 1690 cm^{-1} in the carbonyl region, indicative of the two nonequivalent carbonyl groups (69HCA1810; 70JHC615).



SCHEME 17



64



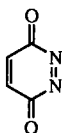
65



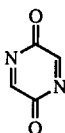
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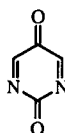
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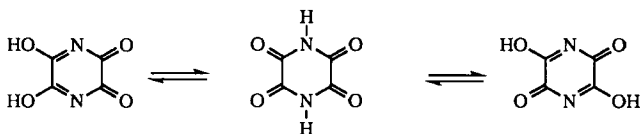
68



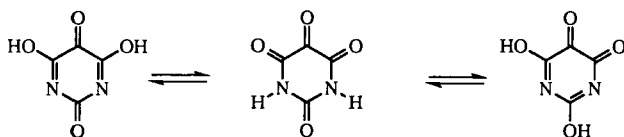
69



70



71



72

IV. Diazabenzquinones

Formally four diaza analogs of *o*-benzoquinone (64–67)) and three diaza analogs of *p*-benzoquinone (68–70) are possible. Since various hydroxy derivatives of these structures (e.g., tetraketopiperazine 71, alloxan 72) differ in both physico-chemical properties and reactivity and are also known to be present primarily in oxo forms, these compounds are not covered in this review.

A. SYNTHESIS

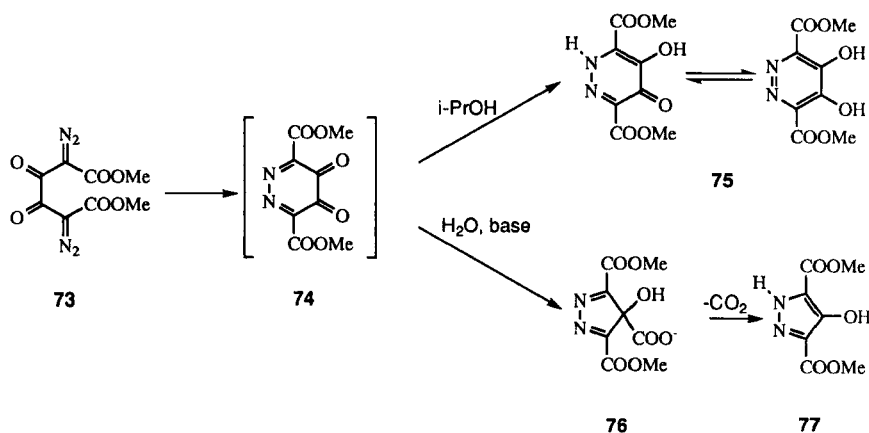
Literature reports on diazaquinones derived from *o*-benzoquinone are very rare. Compound **74** was suggested to be a common intermediate formed during heating of 2,5-bis(diazo)-3,4-diketoadipate **73** with isopropanol and with various bases (76T269). Direct reduction of the intermediate with isopropanol provided pyridazine **75**. A base-catalyzed benzilic acid rearrangement of **74** followed by decarboxylation of **76** afforded pyrazole **77** (Scheme 18).

To the best of the author's knowledge, the only isolated diaza analog of *o*-benzoquinone is bis-*N*-oxide **79** and its derivatives. Compound **79** was isolated as orange-colored crystals from a reaction of tetraketo derivative **78** with dinitrogen tetroxide (76TL1703; 77AP264).

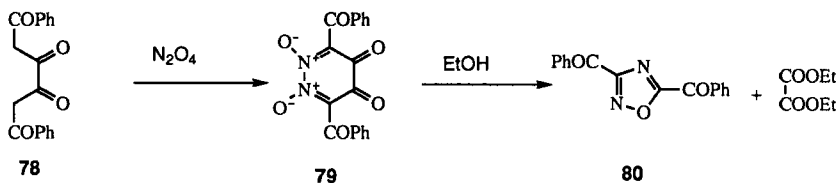
The only diazaquinones derived from *p*-benzoquinone are pyridazinedione **68** and a limited number of its derivatives. Since both the synthesis and the reactivity of these compounds are similar to corresponding "higher" analogs such as phthalazinediones, they will be treated together in Section V.

B. REACTIONS

The only known reaction of compound **79** is its reaction with ethanol leading to ethyl oxalate and 3,5-dibenzoyloxadiazole **80** (Scheme 19). Although the structure of **80** was proven both by ^{13}C NMR and by comparison



SCHEME 18



SCHEME 19

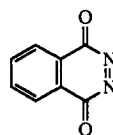
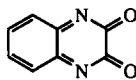
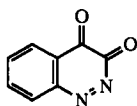
with an authentic sample prepared by a different method, the mechanism of this rearrangement has not been firmly established (76TL1703).

C. Stability and Spectroscopic Properties

A proton-decoupled ^{13}C NMR spectrum of **79** has been reported (76TL1703).

V. Condensed Diazaquinones

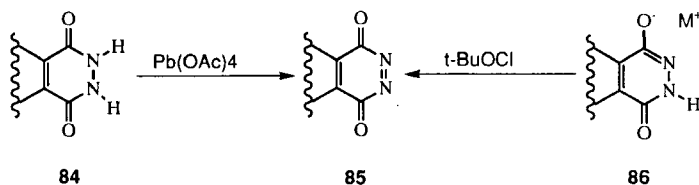
Three different types of condensed diazaquinones, as exemplified by benzo analogs **81**–**83** can be formally anticipated. All reported attempts to prepare **81** have failed to date (76MI1, 76OPP45) and the author is not aware of any reported synthesis of compounds similar to **82**. On the other hand, **83** and other diazaquinones derived from **68** are important both from a theoretical point of view and as intermediates in organic synthesis, and this subject has been partially reviewed (78H1771). In keeping with the consistency of this review, the author has decided to cover the most important achievements in the field as well as all relevant publications that have appeared after the aforementioned review was published. However, additional pertinent information and literature references are cited in the previously mentioned review.



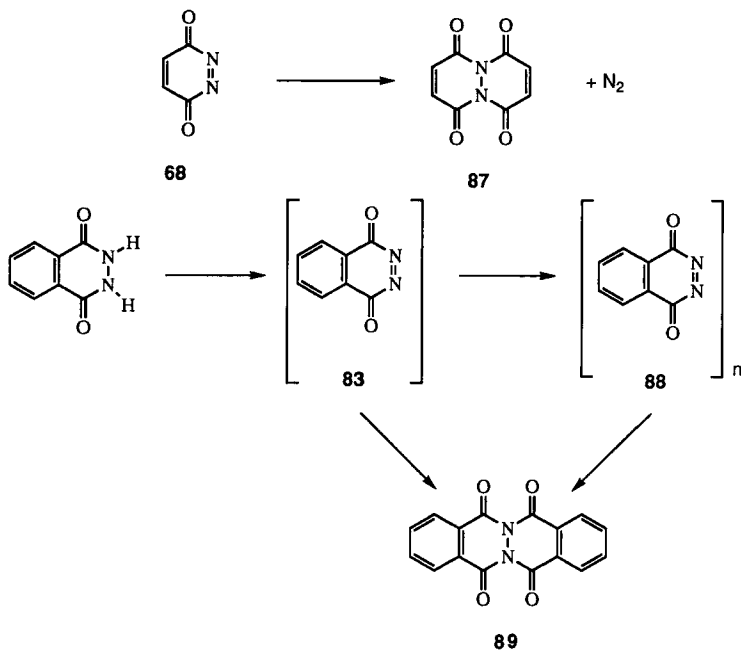
A. SYNTHESIS AND STABILITY

The first synthesis of diazabenzquinones was described by Clement (60JOC1724) and Kealy (62JA966). Clement's procedure is based on the oxidation of the corresponding cyclic hydrazides **84** to diazaquinones **85** with lead tetraacetate at ice bath temperature, usually using acetonitrile as a solvent. Kealy's procedure is based on the oxidation of alkaline salts of the cyclic hydrazides **86** with *t*-butyl hypochlorite in acetone at -77°C (Scheme 20). This method, after filtration of the inorganic salts under an inert atmosphere at low temperature, allows preparation of nearly pure solutions of the diazaquinones. Such solutions can be stored for several hours at -77°C without decomposition. Since the diazaquinones are highly colored, gradual increasing of the temperature allows the study of the stability of diazaquinones.

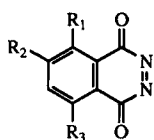
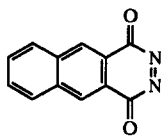
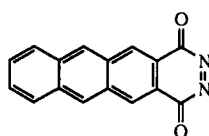
In general, phthalazinediones **68** decompose very quickly at about -30°C , providing compounds **87**. Diazanaphthoquinones are more stable but most cannot be isolated from their solutions. Unsubstituted phthalazinedione **83**, generated *in situ* from phthalic hydrazide at 0°C , gradually decomposes, providing polymeric compound **88** (Scheme 21). Although a successful attempt to isolate **83a** by precipitation from acetone solution has been reported (62JA966), other authors obtained **89** instead. Compound **89** can be also prepared by heating of **88**. Some substituted phthalazinediones are more stable; for example, compounds **83b**, **83c**, and **83d** can be kept in acetone solutions at 5°C without decomposition (74MI4). Diethylamino derivative **83e** was even isolated in the form of deep violet crystals [68AG494]. Polycyclic diazaquinones are usually more stable; e.g., tricyclic compound **90** and tetracyclic **91** can be isolated as maroon and violet crystalline solids, respectively [68AG(E)480; 78JCR(M)3849, 78JCR(S)318]. On the other hand, various diazaquinones having either five-membered or six-membered heterocyclic rings instead of the phthalazinedione benzene ring are less stable than phthalazinediones themselves (69MI1; 71JHC13; 84AJC1001).



SCHEME 20



SCHEME 21

**83a** $R_1 = R_2 = R_3 = H$ **83b** $R_1 = NO_2, R_2 = R_3 = H$ **83c** $R_1 = H, R_2 = NO_2, R_3 = H$ **83d** $R_1 = AcNH, R_2 = R_3 = H$ **83e** $R_1 = H, R_2 = Et_2N, R_3 = H$ **90****91**

B. REACTIONS

Although some diazaquinones can be isolated, these species are generally formed *in situ* by reactions that utilize Clement's procedure (lead tetraacetate in acetonitrile) or Kealy's procedure (*t*-butyl hypochlorite in acetone). Kealy's procedure is preferred when pure solutions of diazaquinones free of inorganic salts and unreacted starting hydrazides are re-

quired. Clement's procedure is valuable due to its simplicity and sometimes also for its higher yields of the final products. Other oxidizing agents have been reported, e.g., chlorine, manganese dioxide, or nickel peroxide, but have not found wider use (68JA532; 70BCJ3926; 86PHA597).

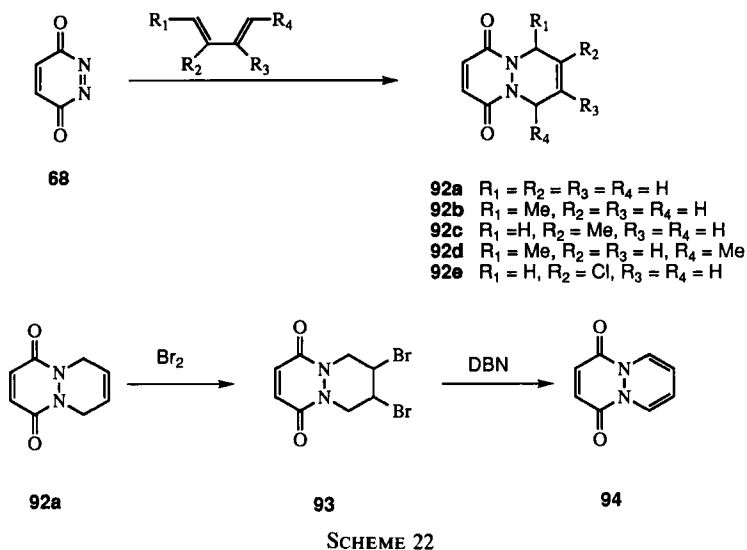
1. *Diels–Alder Reaction*

The exceptional reactivity of diazaquinones toward dienes is probably the most notable property of these compounds. The diazaquinones react rapidly with dienes at -77°C , providing good yields of 1,4-addition products. Dichloromethane, in which diazaquinones are not very stable but are generated very quickly in high yields, is often used as a solvent of choice for the Clement's procedure due to the high reactivity of the diazaquinones toward a Diels–Alder reaction in this solvent (74MI3). Initially Diels–Alder reactions were used to prove that diazaquinones were indeed being formed. Subsequently the high reactivity has been used for other purposes.

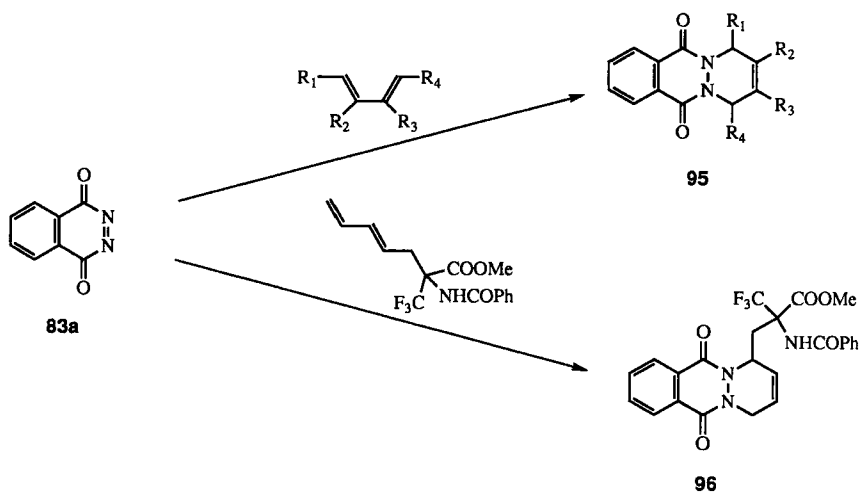
a. *Cycloadditions of Butadiene Derivatives.* The tendency of butadienes to undergo cycloaddition with diazaquinones is well documented in the literature for many diazaquinones, including pyridazinediones, phthalazinediones, and polycyclic compounds. For example, Diels–Alder adducts of 3,6-pyridazinedione **68** and a variety of butadiene derivatives have been reported and some are shown in Scheme 22 (60JOC1724; 62JA966, 62JOC1115; 70BCJ3926; 74AKZ1000; 82MI1). Adduct **92a**, on bromination to **93** and subsequent treatment with DBN provided an interesting bicyclic compound **94**, which was studied as an unusual 10 π -electron aromatic system (72TL1885).

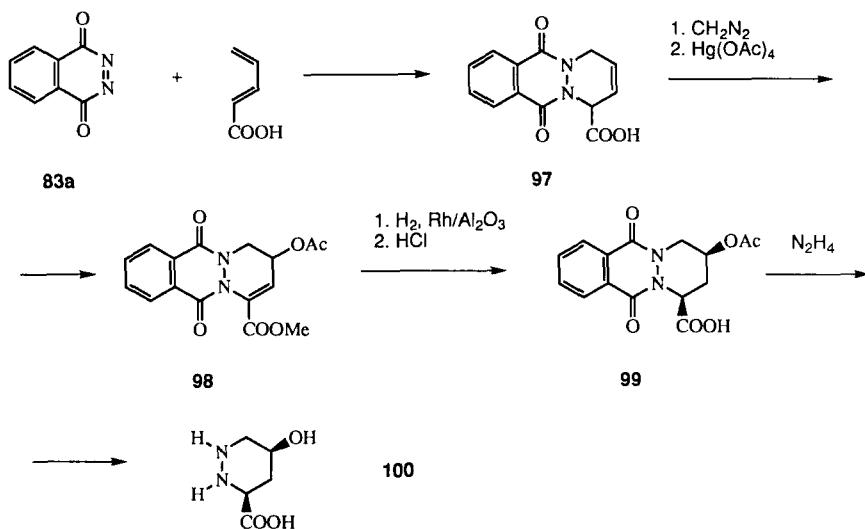
The same behavior toward butadiene derivatives is documented for several bicyclic and polycyclic diazaquinones. Phthalazinedione **83a** when treated with a wide variety of dienes afforded adducts **95** (60JOC1724; 62JA966, 62JOC1115; 70BCJ3926; 75MI3; 76H135). The unusual amino acid derivative **96** was prepared in a similar fashion (Scheme 23) (91CZ292).

A complex naturally occurring amino acid 5-hydroxypiperazic acid (5HyPip) **100** was prepared by a multistep procedure that included Diels–Alder addition of 2,4-pentadienoic acid to phthalazinedione **83a** as a first step (Scheme 24). Adduct **97** was esterified and oxidized with mercuric acetate to **98**, which on hydrogenation over rhodium on alumina and subsequent hydrolysis provided a mixture of enantiomers from which the required enantiomer **99** was obtained by resolution with quinine. Its hydrazinolysis provided **100** [71JCS(C)514; 77H119].



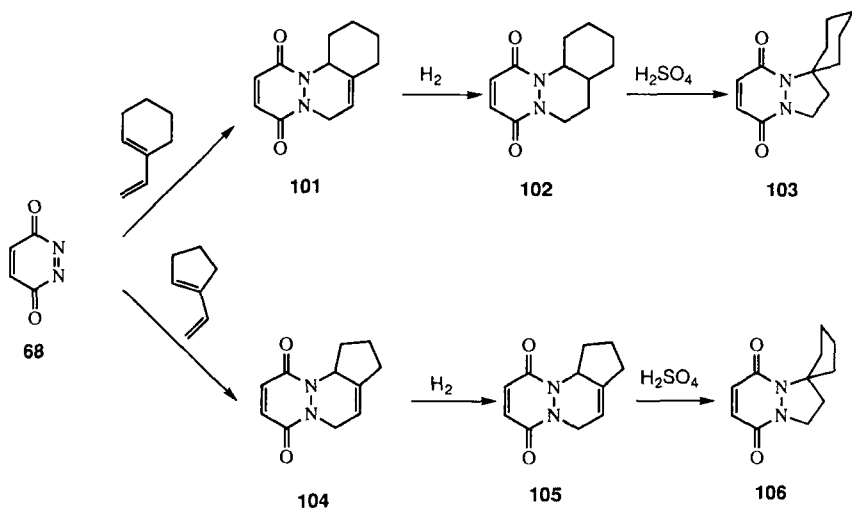
Compounds **101** and **104** were formed by Diels–Alder reaction of **68** with vinylcyclohexene and vinylcyclopentene, respectively (69TL1523; 72MI1). These adducts, after hydrogenation and subsequent acidic treatment with concentrated sulfuric acid, afforded spiro compounds **103** and **106** (Scheme 25).



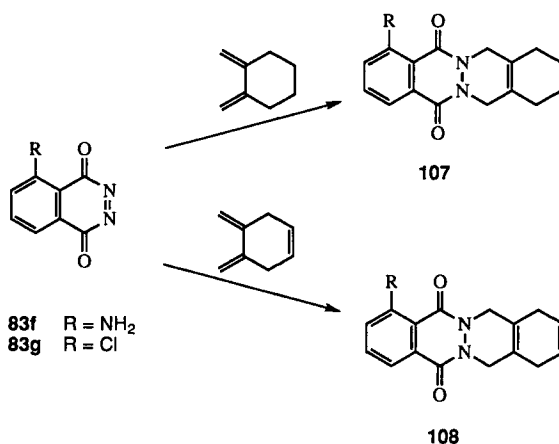


SCHEME 24

1,2-Dimethylenecyclohexane and 1,2-dimethylene- Δ^4 -cyclohexene provided tetracyclic derivatives **107** and **108**, respectively, as depicted in Scheme 26 (74H649; 77H953). Compounds **109**, containing a similar tetracyclic skeleton but with varying placement of the bridgehead nitrogen atoms, were prepared by Diels–Alder addition of butadiene and several



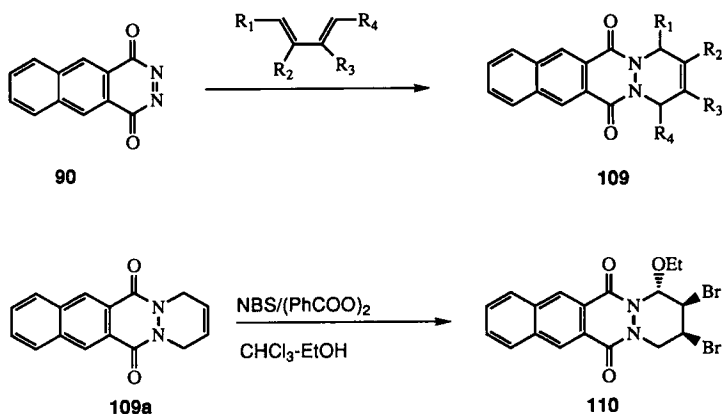
SCHEME 25



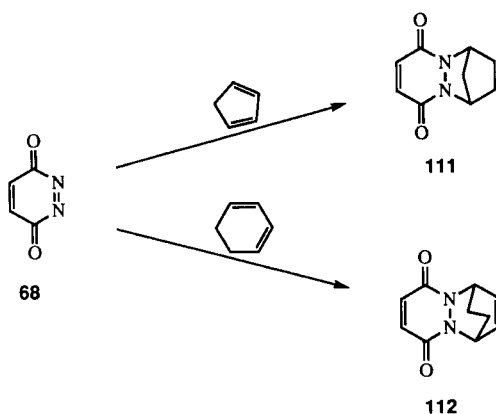
SCHEME 26

substituted butadienes to diazaquinone **90** [77T2109; 82H669; 91JCS(P1)273]. An unusual substitution of the D ring of **109a** leading to **110** occurred by a treatment of **109a** with NBS/benzoyl peroxide in the presence of a small amount of ethanol (Scheme 27) (77T2109).

b. *Additions with Cyclic Dienes.* Cyclic dienes, especially cyclopentadiene and cyclohexadiene, have been employed in the reaction with pyridazinedione **68**, providing compounds **111** and **112** and/or their derivatives (Scheme 28) (62JA966; 67BCJ2446; 74MI4; 83CB1897). In addition to substituted phthalazinediones, some heterocyclic analogs were used

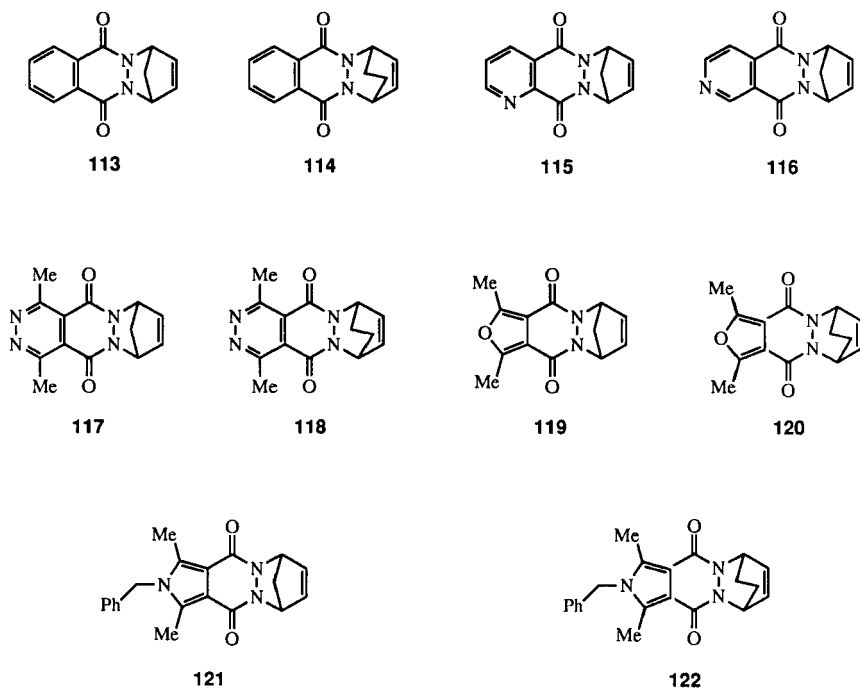


SCHEME 27



SCHEME 28

for the reaction, which afforded compounds **113–122** [71JHC13; 73JCS(P1)26]. Clement's procedure was used in these cases and acidic nitrogen atoms of pyrrole derivatives needed to be protected, e.g., by a benzyl group; otherwise a complex mixture is formed.

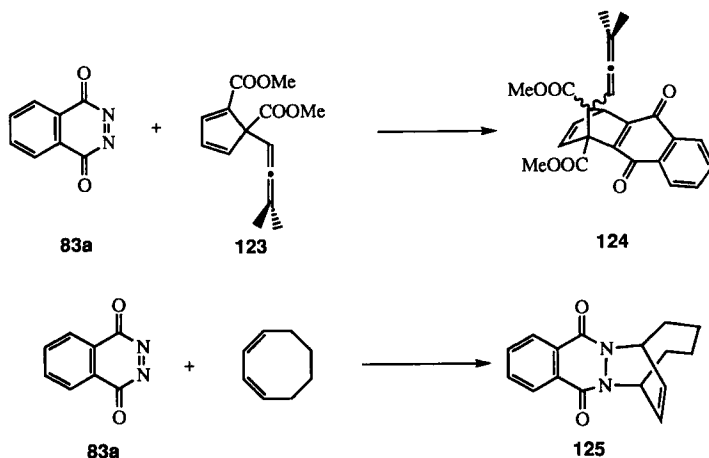


The potent dienophilic character of the diazaquinones has been demonstrated, in that phthalazinedione **83a** reacted with some dienes known to be resistant toward Diels–Alder addition (Scheme 29). Diene **123**, deactivated both by a bulky substituent and by the 1-methoxycarbonyl substituent, provides **124** below room temperature (73JA8380). Phthalazinedione **83a** reacts even with cyclooctadiene (Scheme 29), providing compound **125** at 0°C (66JOC3862).

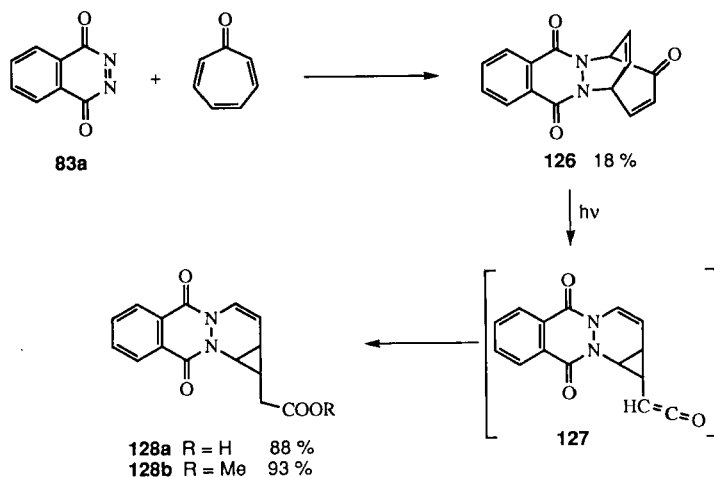
Reaction of phthalazinedione **83a** with tropone provided adduct **126**, which was photochemically transformed into acid **128a** in acetonitrile–water solution at room temperature, or to its methyl ester **128b** when the reaction was performed in methanol (Scheme 30). Ketene **127** was implicated as the primary intermediate on irradiation and the final products of addition of water and/or methanol **128a** and **128b**, respectively, were isolated in high yields [72JCS(P1)783].

c. Additions with Aromatic Compounds. Diazaquinones react with anthracene to provide products resulting from addition onto the C-9,10 positions, as revealed by the structure **129**. The analogous reaction has been documented for pyridazinedione **68**, some phthalazinediones **83**, and polycyclic diazaquinones [62JOC1115; 73CC248; 80JCS(P1)1841]. Diazaquinones possessing variously fused heterocycles usually provide low yields of these adducts [68JCS(C)2857; 80JCS(P1)1834].

Phthalazinedione **83a** reacts with perylene derivatives anomalously to provide polycyclic pyridazine derivatives (82S854). Dibenzoperylene **130** provided 67% of pyridazine **133**, probably via Diels–Alder adduct **131**,



SCHEME 29

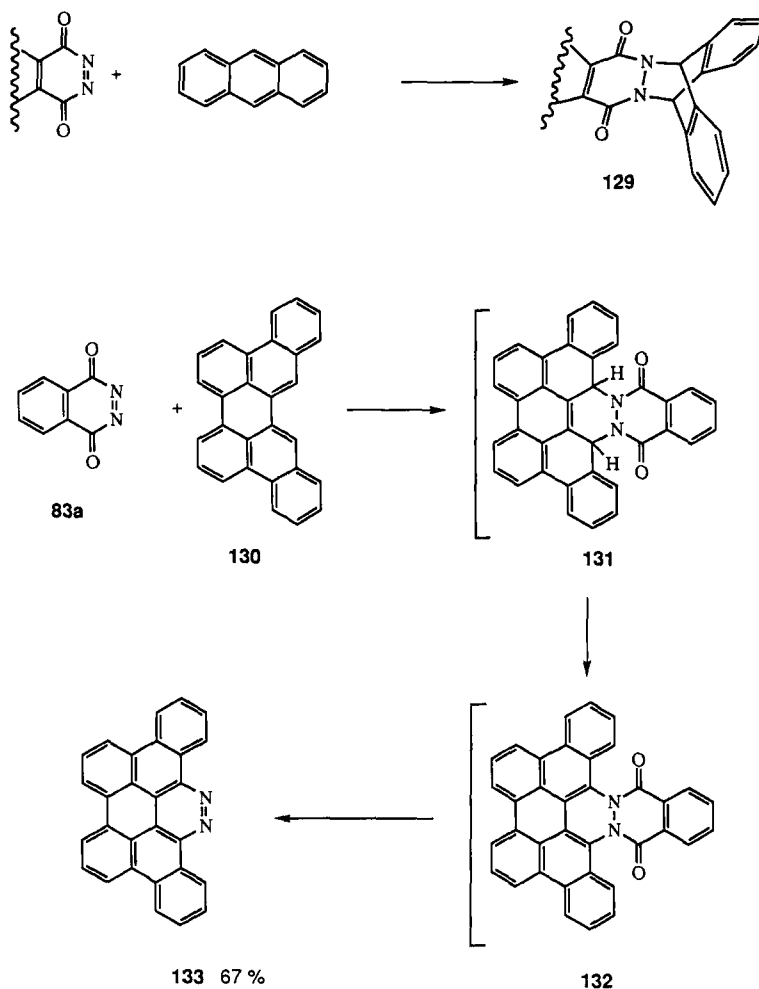


SCHEME 30

which was further oxidized to **132** and then stabilized to the final product **133** (Scheme 31).

d. *Additions with Heterocyclic Dienes.* *N*-Alkyl-2-pyridones have been also successfully used as dienes in the Diels–Alder trapping of diazaquinones, which is evident by providing compounds **134a–134c** (Scheme 32) (76JHC673). Attempts to utilize other potential heterocyclic dienes, e.g., furan or *N*-methylpyrrole, did not provide Diels–Alder adducts (78H1771). Although the Diels–Alder reactions of various heteroatom substituted dienes with quinones have been studied extensively (88MI2), the reaction of *N*-alkyl-2-pyridones with diazaquinones is the only successful report of this type of addition.

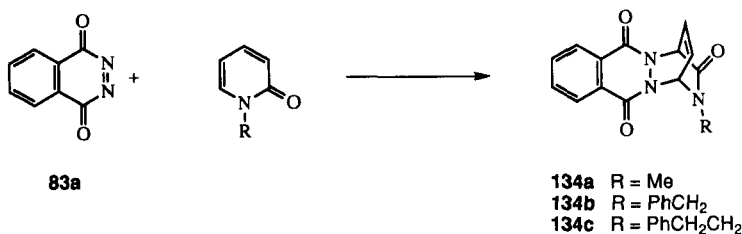
e. *Use of Diels–Alder Addition for Protecting a 1,3-Diene System.* Protection of a diene system by cycloaddition with suitable dienophiles is an attractive method for stereospecific structural modifications. Use of diazaquinones in this strategy offers some advantages in that diazaquinones are very reactive and their adducts are compatible with various reaction conditions. The range of dienes that can be protected by this method is limited to compounds having substituents compatible with the reaction conditions under which diazaquinones are generated. For example, some terpenoids have produced high amounts of polymeric material (87H193; 89H791). In some cases anomalous reaction products are formed. An interesting example, as depicted in Scheme 33, shows that the product



SCHEME 31

of reaction of diazaquinone **90** with citral derivative **135** is hydroxy derivative **138** and not the expected product **136** (89H791). Another obstacle is a very limited choice of deprotection conditions known.

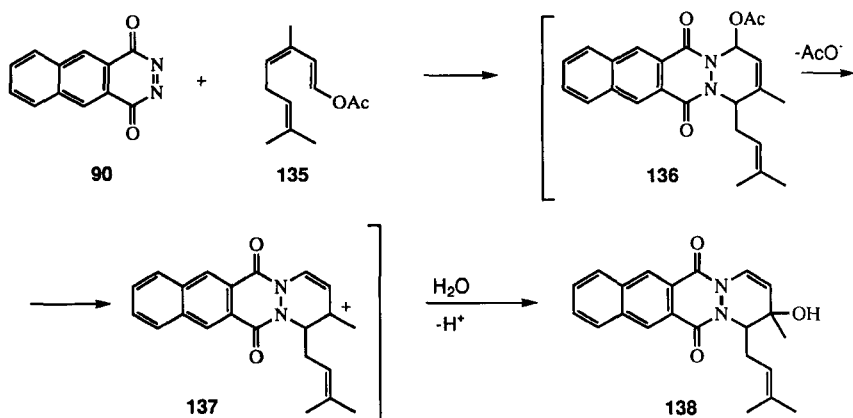
Diazaquinones **68**, **83a**, and **90** have been shown to provide adducts with various isoprenoids, as exemplified by the β -myrcene adduct **140** (87H193). The side-chain double bonds of these adducts can be functionalized by epoxidation with 3-chloroperoxybenzoic acid or via bromination with *N*-bromosuccinimide to provide the corresponding derivatives **141** and **142**, respectively (Scheme 34).



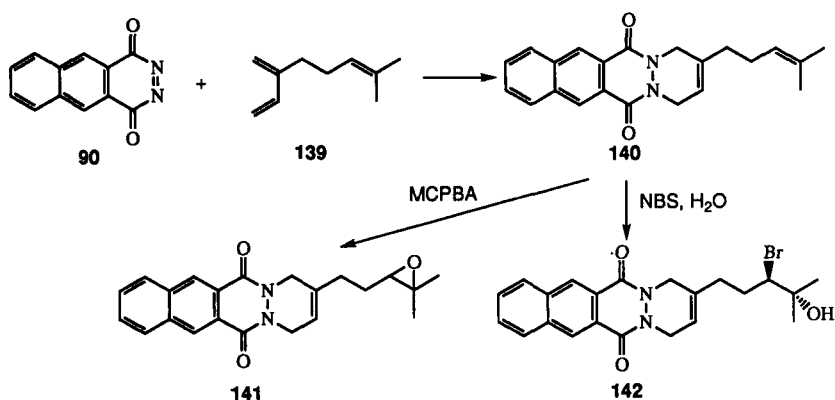
SCHEME 32

The use of Diels–Alder adducts of diazaquinones for protecting of steroidal 14,16-dienes, e.g., **143**, has been reported (68CC1434). Both isomers were isolated, but compound **145** prevailed (Scheme 35).

In this context the addition of diazaquinones to ergosterol derivatives has been studied [73JCS(P1)888; 78ZOB897, 78ZOB908; 79ZOB227; 81ZOR1909; 86PHA597]. The reaction of ergosterol acetate **146** with pyridazinedione **68** provided adduct **147**, which, when treated with ethanolic potassium hydroxide, efficiently liberated ergosterol in high yield. Oxidation of adduct **147** with ozone and subsequent reduction afforded aldehyde **148**, which provided the Wittig adduct **149** (Scheme 36). However, attempts to reduce selectively the side-chain double bond failed. The double bond in the pyridazine ring was more easily reduced, providing **150**, which then underwent steroid ring double bond reduction to **151** [73JCS(P1)888; 81ZOR1909]. Using phthalazinedione **83a** instead of **68** enabled deprotection of the corresponding benzo analog of **149** by its reduction with lithium



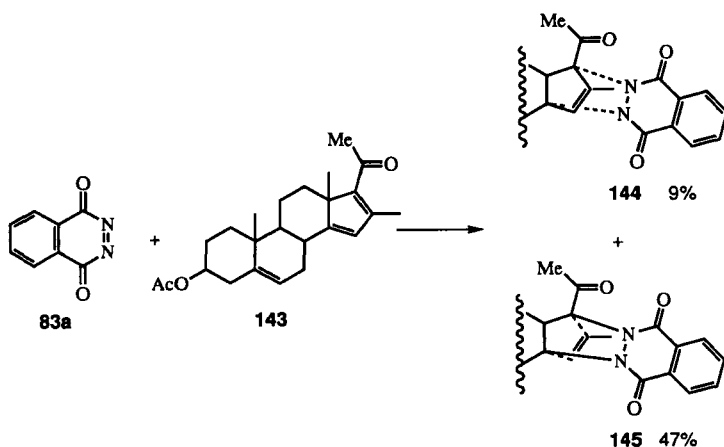
SCHEME 33



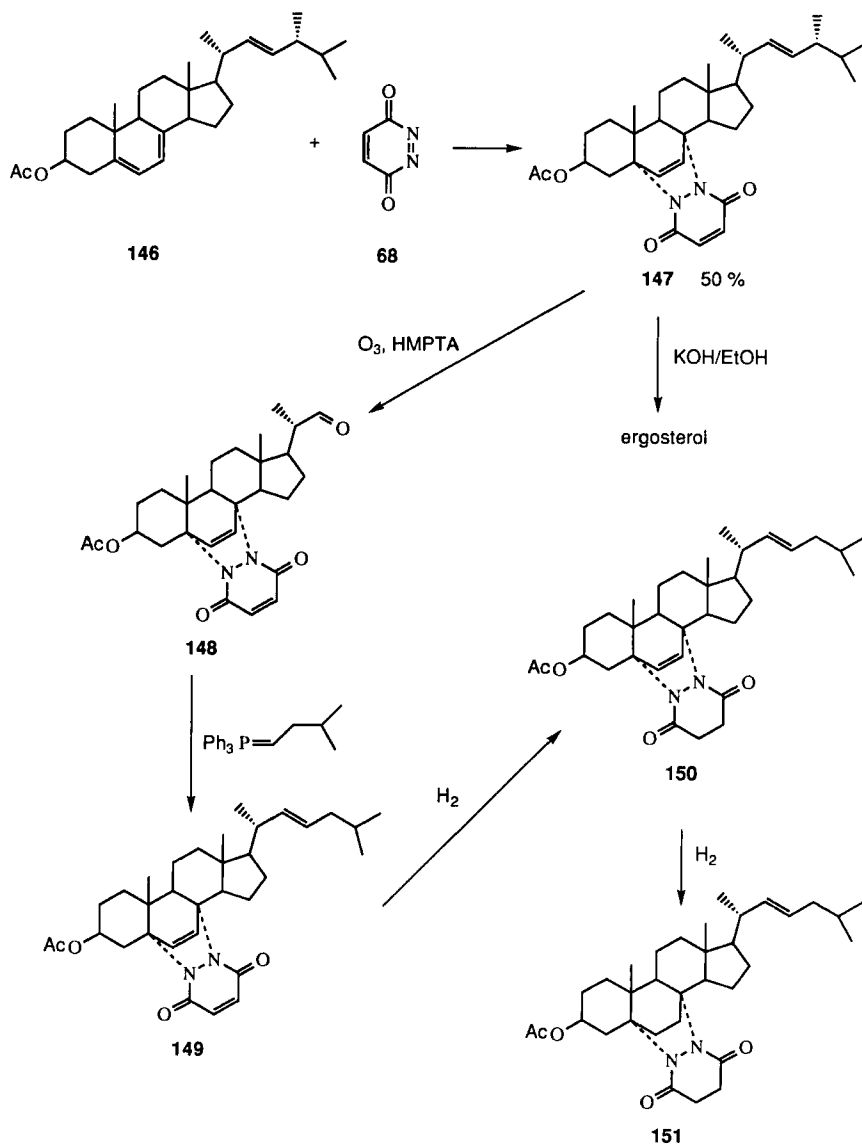
SCHEME 34

aluminum hydride. Δ^{22} -*trans*-Cholesta-5,7,22-triene-3- β -ol was prepared from ergosterol acetate in 36% overall yield (78ZOB908).

The concept of using diazaquinones for diene system protection was accomplished in the case of some vitamin D derivatives, as shown in Scheme 37 (86JOC4819). Acetyl vitamin D₂ **152** was protected with phthalazinedione **83a**, providing a mixture of both possible stereoisomeric adducts from which **153** was isolated. Then usual ozonolysis procedure afforded aldehyde **154**, which after the Wittig coupling and hydrogenation provided **155**. The most difficult part of the sequence proved to be the deprotection of this compound, but this transformation was accomplished

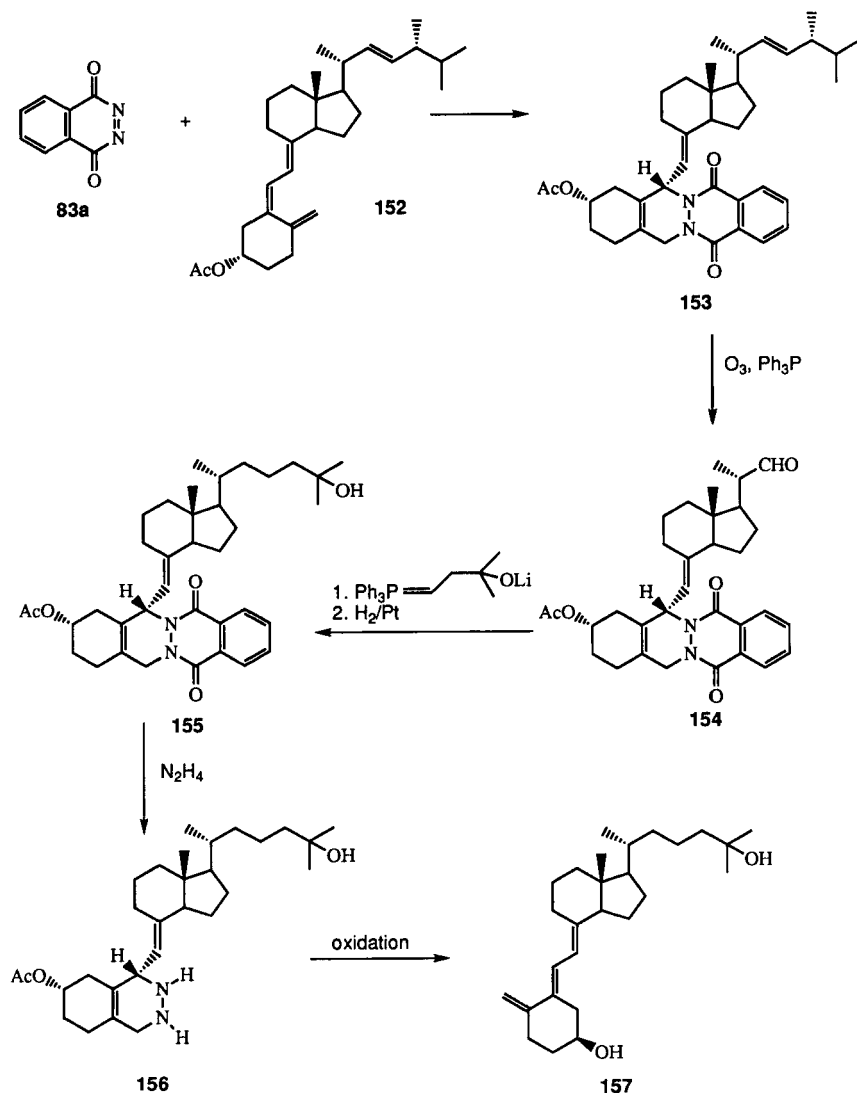


SCHEME 35



SCHEME 36

by hydrazinolysis followed by oxidation of the intermediate **156**. Sodium periodate or, more effectively, dianisyl telluroxide was used as oxidant. This reaction proceeds via the corresponding azo compound and provides 25-hydroxy-5,6-*trans*-vitamin D₃ **157**.



SCHEME 37

2. 1,2-Addition

1,2-addition was reported to take place during the addition of pyridazinedione **68** to styrene (71LA96). The proposed primary adduct **158** is stabilized by addition of water, *t*-butanol, or acetic acid, which are formed

in the reaction mixtures depending on the procedure used to provide products **159** (Scheme 38). Phthalazinedione **83a** also afforded the 1,2-addition product as a main product, but **161** was also isolated. The formation of this compound can be rationalized as follows. Primary 1,4-adduct **160** is stabilized by reaction with another molecule of the diazaquinone, which results in the formation of the final product **161** (Scheme 39) (71LA96). A similar reaction was also described for methylstyrene, which provided the corresponding methyl derivative of **161** (77MI2).

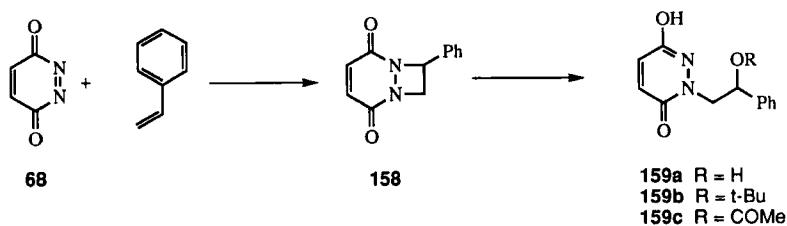
The only reported 1,2-addition providing a relatively stable adduct is that of a 1,2-cycloaddition of phthalazinedione to indene (Scheme 40). Compound **162** was isolated and characterized (66JOC3862; 71CC695). A similar 1,2-addition reaction to the 9,10-double bond of phenanthrene was also reported but not firmly documented (66JOC3862).

3. Nucleophilic Reactions

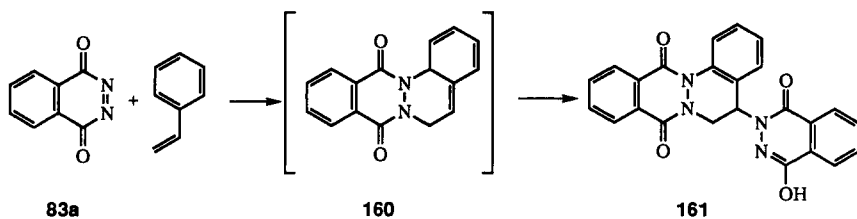
Diazaquinones are very sensitive to the nucleophilic addition of water thereby leading to the formation of dimeric compounds. Thus, pyridazinediones **68** provide **163**, the corresponding maleic anhydride **164**, and nitrogen (62JA966). Phthalazinedione **83a** gave **165** likely in the same manner (Scheme 41).

3-Aminocrotonate **166** reacted with phthalazinedione **83a** to afford compound **167**, which on acidic hydrolysis produced the acetyl derivative **168** (77MI3). Similarly, enaminoester **169** led to compound **170** (77CB1716). The imino group of **170** can be hydrolyzed under mildly acidic conditions to an oxo group to provide **171**. Alkaline hydrolysis is accompanied by decarboxylation affording **172** (Scheme 42).

Additions similar to those described in this section can occur as a secondary transformation in the reaction of phthalazinedione with styrene, which has been described earlier and is depicted in Scheme 39.



SCHEME 38

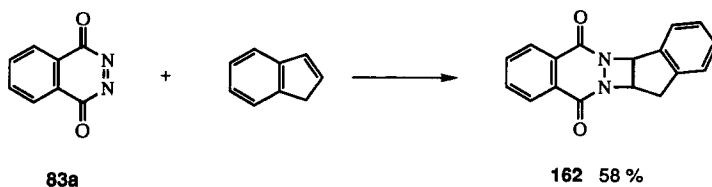


SCHEME 39

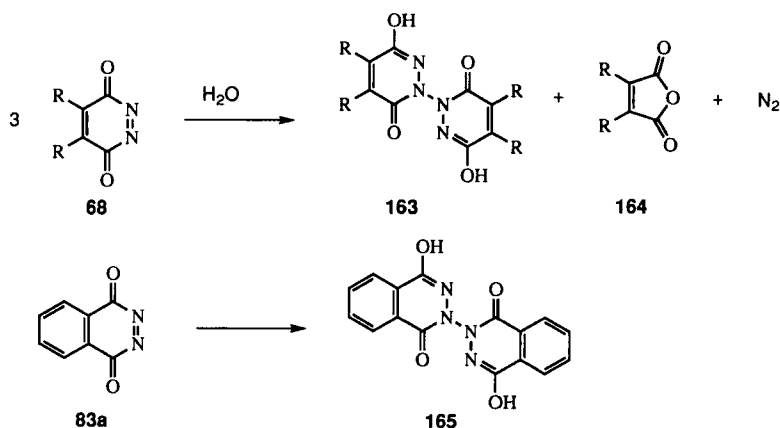
4. Miscellaneous Synthetic Applications

Phthalazinedione **83** theoretically can extrude nitrogen and subsequently an allowed $[\sigma 2s + \sigma 2s + \sigma 2s]$ fragmentation would give bis-ketene **173** that would be able to rearrange to benzocyclobutenedione **174**, as shown in Scheme 43 [71CC695]. However, phthalazinedione **83** is not stable enough and readily decomposes by the pathway discussed earlier, as shown in Scheme 21, and therefore its use for the synthesis of **174** is not possible. Fortunately, flash vacuum pyrolysis of its 1,4-adducts with various dienes or the 1,2-adduct with indene regenerates the diazaquinone, which under specific conditions provides the required compound **174** (Scheme 44) [71CC695; 73CC248; 77JOC2371; 80JCS(P1)1834, 80JCS(P1)1841]. Jung and Lowe reported yields of 88 and 64%, respectively, for this pyrolysis performed at 500°C [77JOC2371]. This method of preparation of benzocyclobutenediones has been proven useful for a variety of substituted compounds such as the dimethoxy derivative **176** (Scheme 44). Adducts with anthracene seem to be the starting materials of choice and the pyrolysis of their vapors at 450°C gave the best results [73CC248; 80JCS(P1)1834, 80JCS(P1)1841]. For example, Abou-Teim *et al.* compared yields from the pyrolysis of various adducts for the synthesis of **176** and then obtained the product from the anthracene adduct **175** in 98%, compared to 12% from the corresponding cyclopentadiene adduct [80JCS(P1)1841].

Substituted phthalazinediones can be easily prepared from the corresponding phthalic anhydrides via their hydrazides. Since many phthalic

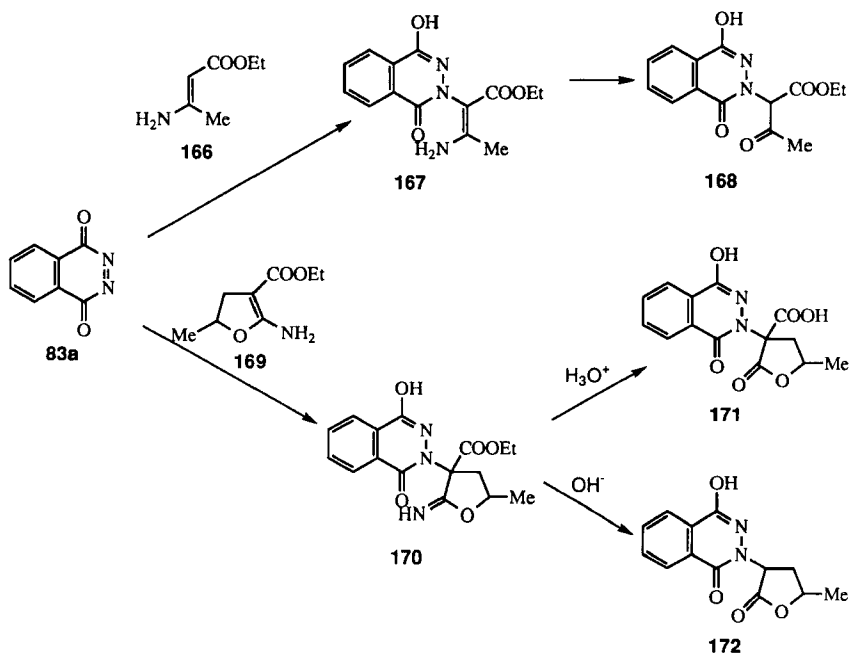


SCHEME 40

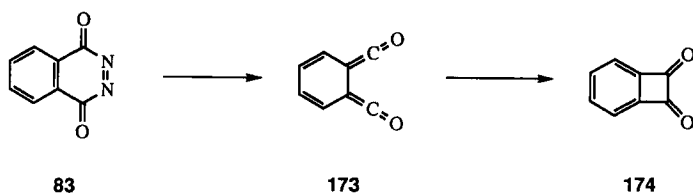


SCHEME 41

anhydrides are either commercially available or can be easily prepared, this method of preparation of benzocyclobutenediones is especially attractive and has been often used. High yields of the benzocyclobutenediones bearing halogen, methyl, or methoxy substituents can be obtained. Unfor-



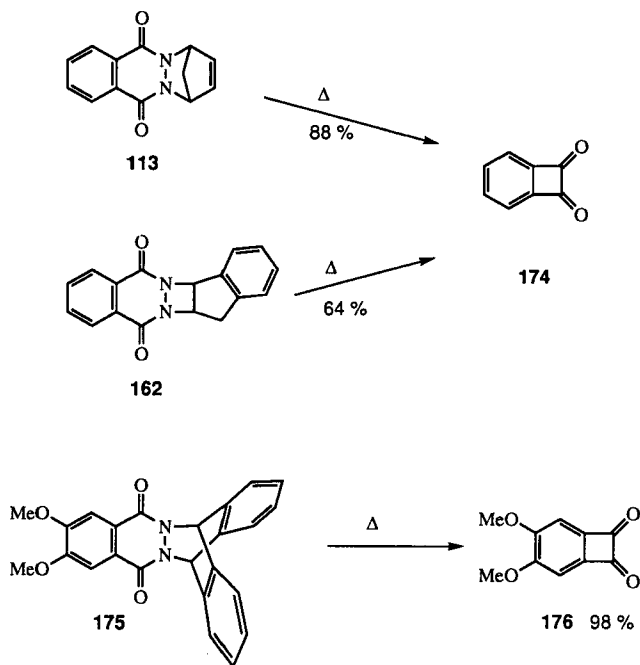
SCHEME 42



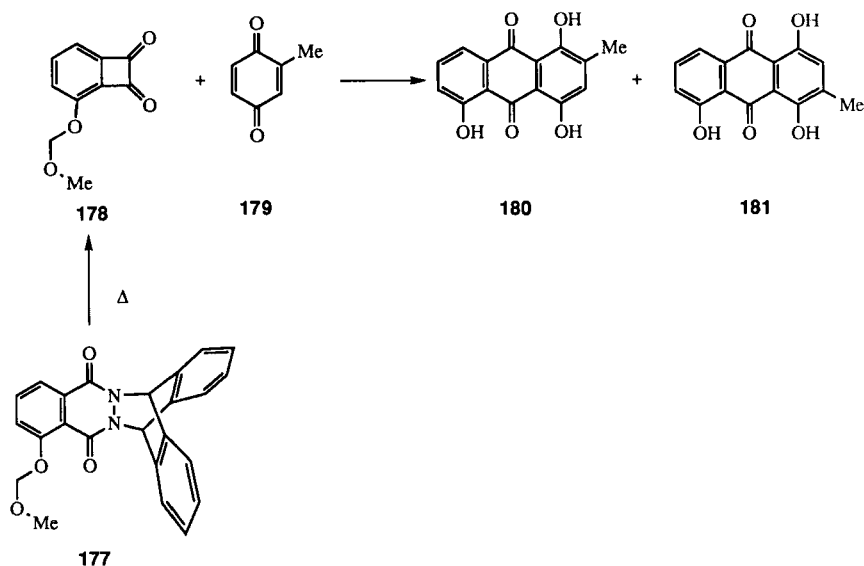
SCHEME 43

tunately, for various heterocyclic analogs, very low yields, at best, have been reported [80JCS(P1)1834].

Benzocyclobutenediones are of interest on their own as well as for their usefulness as versatile intermediates. The synthesis of adriamycin analogs has been attempted and the syntheses of the similar tricyclic natural products islandicin **180** and digitopurpurone **181** (Scheme 45) are examples of this approach (77JOC2371).



SCHEME 44



SCHEME 45

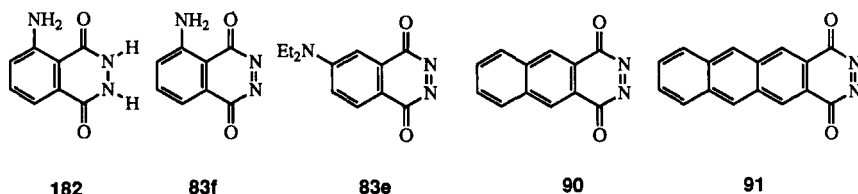
C. SPECTROSCOPIC PROPERTIES

Most diazaquinones are not sufficiently stable to allow definitive spectroscopic studies. However, the IR and UV spectra of tetracyclic diazaquinone **91** have been reported (68JA5932). The electronic spectra of **68**, **83a**, and **90** formed in solution show maximum absorption to be at 260, 360, and 450 nm, respectively (86JA7716).

D. CHEMILUMINESCENCE

Chemiluminescence results from the emission of light from electronically excited molecules, whose excitation is produced from a chemical reaction by a direct energy transformation. Although such light emission has been observed from a variety of chemical reactions, the most prominent example of nonbiological liquid phase chemiluminescence remains the oxidation of dicarboxylic hydrazides represented by luminol **182**. Long before the first diazaquinones were synthesized by Clement and Kealy, Albrecht suggested that compounds of this type could be active chemiluminescent intermediates (28M11). The similarity of chemiluminescence characteristics for luminol and some stable diazaquinones (e.g., **83e**, **90**, **91**)

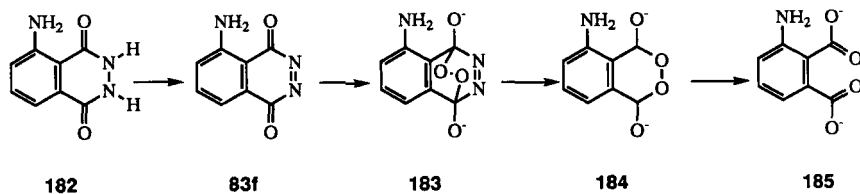
suggested an involvement of **83f** in the luminol chemiluminescence [68AG494; 69JOC2462; 78JCR(M)3849, 78JCR(S)318]. Studies on chemiluminescence often used the rapid Diels–Alder reaction of diazaquinones with cyclopentadiene (67BCJ2446; 68JA5932; 78JCR(M)3849, 78JCR(S)318). The addition of dienes to various chemiluminescent systems based on the oxidation of cyclic hydrazides has been shown to halt the luminescence and isolated adducts proved that diazaquinones are intermediates in the process.



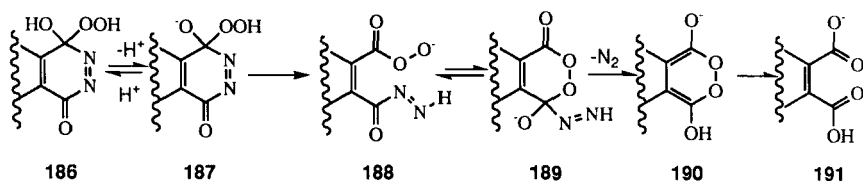
Since diazaquinones alone do not show chemiluminescence and an additional oxidant is necessary for the chemiluminescence, the diazaquinones are believed to be intermediates in the process. Rauhut suggested that peroxide **183** is the key intermediate; its decomposition was the light-releasing step (66JOC2431). Michl proposed a mechanism of decomposition of **183** through nitrogen extrusion and formation of intermediate **184** (Scheme 46) (75JPC125; 77MI1). An alternative mechanism, depicted in Scheme 47, which involves peroxide **186** rather than generally accepted intermediate **183**, has been reported [81JCS(F1)2137; 86JA7716].

VI. Bridgehead Nitrogen Atom-Containing Quinones

There is no question that compounds discussed in this review so far comply, at least formally, with a common understanding of the nature of quinones. However, bridgehead compounds of general formulae **192–194**, where A,B,C, is CH or N raise new and interesting issues. The author's view that these compounds can be included in the azaquinone family is

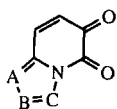
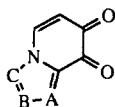
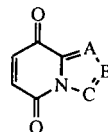


SCHEME 46



SCHEME 47

supported by Trost's comprehensive definition of quinones, which was cited by Turney in his review on nonbenzenoid quinones (74MI2). Trost defined quinones to be any dicarbonyl species whose 2-electron reduction product generates an aromatic system. A simple extension of this definition to the heteroaromatic field justifies the author's view, since 2-electron reduction products of these structures have 10 electrons (including 2 non-valent nitrogen electrons) and conform to Hückel's $4n + 2$ -electron rule. Of course, the same is true for annulated derivatives possessing an additional bridgehead nitrogen conforming to structures **192**–**194**. Such tricycles would be expected to afford 14-electron systems on reduction and therefore also conform to Hückel's rule.

**192****193****194**

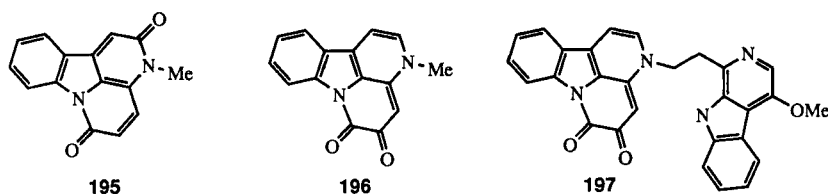
A. CANTHIN-4,5-DIONE ALKALOIDS AND THEIR DERIVATIVES

To the best of my knowledge, canthin-4,5-diones are the only known representatives belonging to the class of bridgehead nitrogen containing quinones represented by **192**. A literature search did not reveal any compounds containing fragment **193**.

1. Historical Background

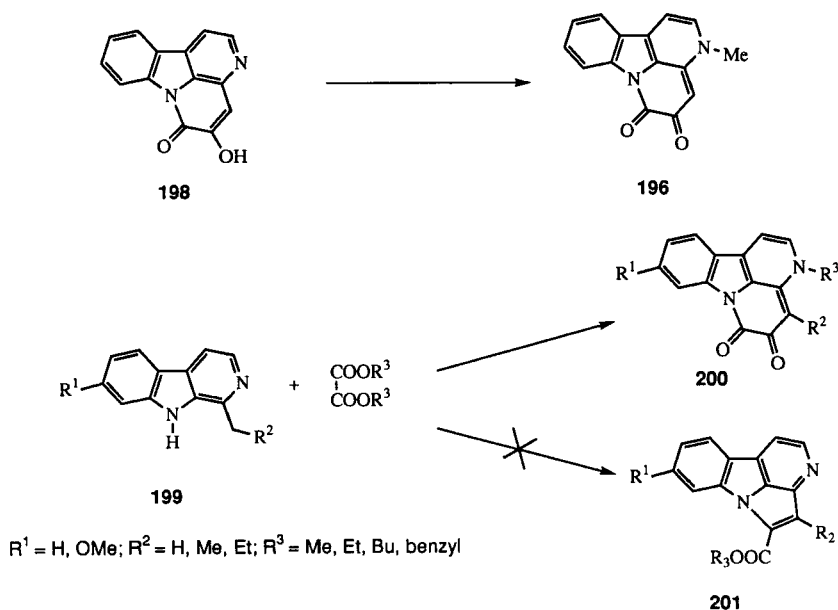
The wood of *Picrasma quassioides* (Bennet) has been used medicinally in Japan. Several β -carboline and canthin alkaloids, including Picrasidine L and M, have been isolated from this wood. Some of these substances and their derivatives have adenosine 3',5'-cyclic monophosphate phosphodiesterase-inhibiting activity (82CPB1204; 83CPB3198; 84CPB1872; 85CPB3847; 88CPB4588). Originally formula **195** was attributed for Picras-

idine L, but the correct formula **196** was finally established (85CPB3847). Picrasidine M **197** contains the same quinonoid portion as Picrasidine L.



2. Synthesis of 3alkyl-3H-5,6-dihydro-5,6-dioxindolo[3,2,1-de][1,5]naphthyridines (Canthin-5,6-diones)

Picrasidine L was first synthesized by methylation of 5-hydroxycanthin-6-one **198**, which was obtained from natural sources (85CPB3847). In 1985 Matus and Fischer found that reaction of 1-alkyl- β -carboline **199** with an excess of dialkyl oxalates at 155–175°C provided *N*-alkylcanthin-5,6-diones **200** (85TL385). This simple one-step reaction opened access to naturally occurring congeners of this class as well as new derivatives. Originally pyrrolizine derivatives **201** were incorrectly reported as products of this reaction (Scheme 48) [80S372; 82ZN(B)762].



SCHEME 48

3. Reactions

3-Alkylcathin-5,6-diones are fairly resistant to acidic hydrolysis, but are easily hydrolyzed under basic conditions. For example 3-ethyl derivative **202** gave green-colored 1-methyl-2-ethyl-2*H*-pyrido-[3,4]indole **203** (Scheme 49) (85TL385).

4. Physicochemical and Spectroscopic Properties

Infrared spectra show two strong absorption bands at about 1680–1695 and 1630–1655 cm^{-1} (85CPB3847; 88CPB4588). Ultraviolet, MS, ^1H NMR, and ^{13}C NMR spectra of Picrasidine L and Picrasidine M have been reported (82CPB1204).

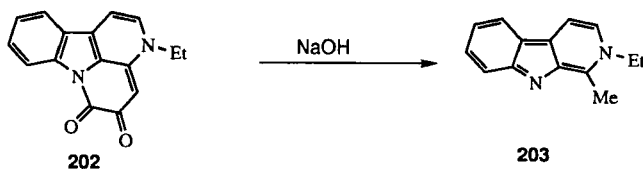
All described compounds of this type are stable at room temperature and have low solubility in common solvents.

B. AZAQUINONES CONTAINING ONE BRIDGEHEAD NITROGEN ATOM

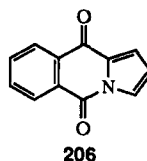
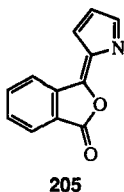
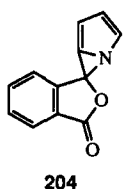
There are only a few examples of bicyclic structures **194** described in the literature. On the other hand, similar tricyclic analogs containing one bridgehead nitrogen atom are not rare and some typical examples will be described here.

1. Synthesis

a. *Pyrrolo[1,2-*b*]isoquinoline-5,10-diones*. The simplest tricyclic azaquinones containing one bridgehead nitrogen atom are pyrrolo[1,2-*b*]isoquinoline-5,10-diones of a general formula **206**. These compounds, earlier called pyrrolene-phthalides, are formed by heating pyrroles with phthalic anhydride. After their discovery, (1884CB2944) structures **204** to **206** were suggested. Finally, the correct structure **206** was assigned to the parent compound by Cornforth and the two alternatives preferred by



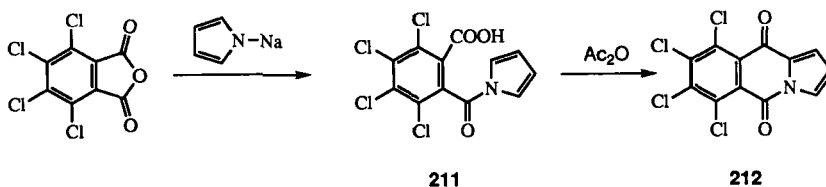
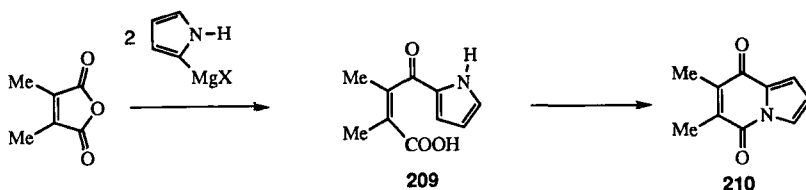
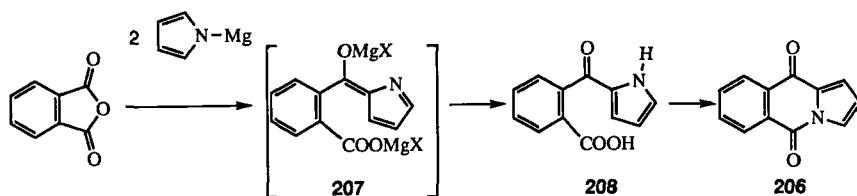
SCHEME 49



earlier investigators were eliminated by the IR spectrum of the compound, which contains a strong amidic bond at $1705\text{--}1708\text{ cm}^{-1}$ and another bond at $1650\text{--}1655\text{ cm}^{-1}$, which corresponds to the other carbonyl group (58JCS1091).

The original synthesis of **206** was performed by heating pyrroles with phthalic anhydride and acetic acid in a sealed tube. Oddo and co-workers prepared "pyrrolene-phthalides" in various ways from pyrrolylmagnesium bromides and phthalic anhydride or 3,3-dichlorophthalide (23G265; 25G235; 34G289, 34G714).

A similar two-step procedure was developed later (Scheme 50). In the



SCHEME 50

first step, two equivalents of the pyrrolylmagnesium bromide reacts with one equivalent of phthalic anhydride to provide the corresponding acid **208**, which was subsequently heated with aqueous ammonia to provide the required compound **206**. When pyrrolylmagnesium halide is formed *in situ* by a reaction of the pyrrole with ethylmagnesium halide, only one equivalent of the pyrrole is required [90JCS(P1)1459, 90JCS(P1)1463]. When aqueous alkaline acetate was used in the condensation step instead of ammonia, the cyclization was much faster.

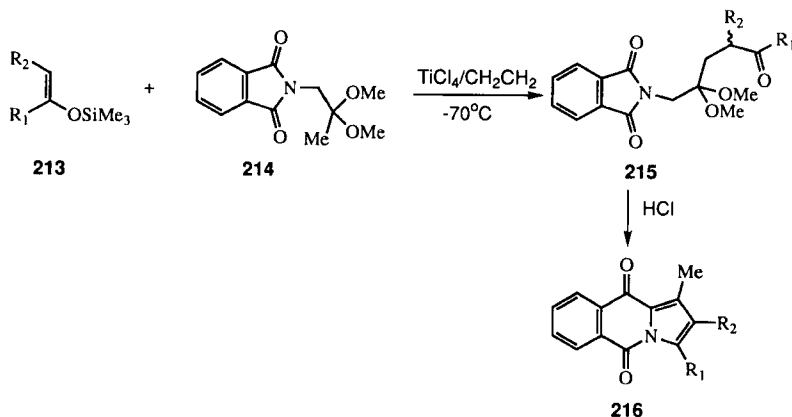
The first successful attempt to prepare bicyclic indolizinedione derivatives **210** was achieved by the reaction of dimethylmaleic anhydride with pyrrolylmagnesium bromide followed by the cyclization of the intermediate acid. The corresponding unsubstituted desmethyl compound cannot be prepared this way [90JCS(P1)1463].

The most efficient synthesis is based on the reaction of phthalic anhydride with the sodium salt of the pyrrole; the intermediate acid after cyclization generally provides high yields of **206** and/or its substituted derivatives. Tetrachloro derivative **212** was prepared from tetrachlorophthalic anhydride via acid **211** by this procedure [90JCS(P1)1463].

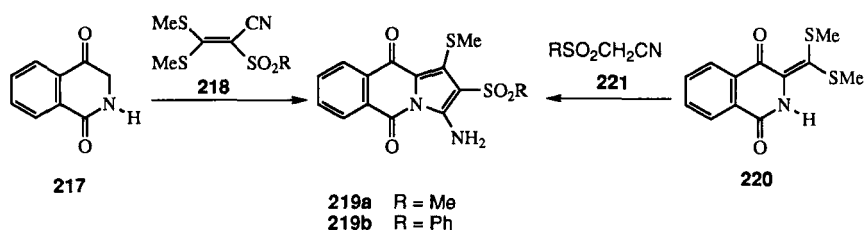
Aldol condensation of silyl enol ethers **213** with **214** provided in good yields the condensation products **215** which on treatment with concentrated hydrochloric acid in methanol gave derivatives **216** (Scheme 51) (88S381).

Substituted derivatives **219** were prepared from 1,2,3,4-tetrahydroisoquinoline-1,4-dione **217** and sulfonyl ketene thioacetals **218**. The same products were also obtained from **220** and **221** (Scheme 52) (79YZ1234).

The benzo analog of **206**, i.e., **223**, was obtained as a main product



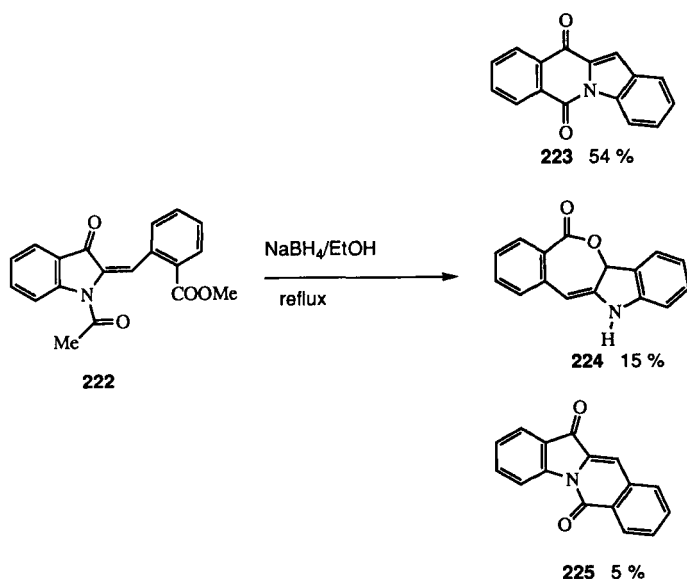
SCHEME 51



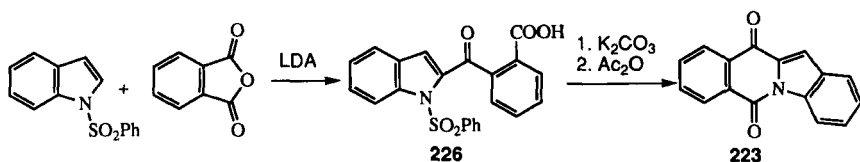
SCHEME 52

when compound **222** was treated with sodium borohydride in refluxing methanol (Scheme 53). Compounds **224** and **225** were also isolated and characterized (93H1287). Compound **223** was also prepared from *N*-benzenesulfonylindole and phthalic anhydride via intermediate **226** as shown in Scheme 54 (93H1287).

b. *Pyrazolo[1,5-a]pyridine-4,7-diones*. Reaction of pyrazole complexes **227** with acetylene derivatives provided intermediates **228**, which after an oxidative treatment with ceric ammonium nitrate provided **229**. The best yields were obtained with disubstituted acetylenes, as terminal acetylenes were less effective. The starting pyrazole carbene complexes



SCHEME 53

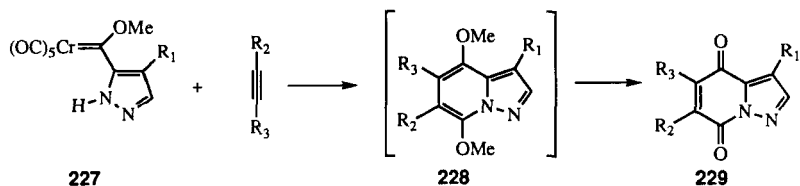


SCHEME 54

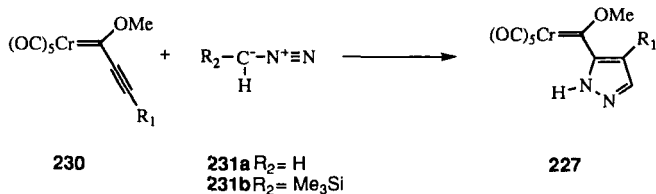
227 were prepared from alkynyl carbene complexes **230** and diazomethane derivatives **231** (Scheme 55) (86JA5229; 87CS517).

c. *Imidazo[1,2-b]isoquinoline-5,10-diones*. Condensation of equimolar amounts of phthaloyl dichloride with imidazoles or benzimidazoles provided tricyclic and/or tetracyclic compounds **232** and **233**, respectively (Scheme 56) (76JOC836). Compound **233** had been previously prepared by oxidation of 2-benzylimidazole **234** with chromium trioxide (66JOC1498) or by acidic hydrolysis of **236** (Scheme 57). Compound **236** was prepared by treatment of compound **235** by 4-nitroso-*N,N*-dimethylaniline. Intermediate **235** can be easily prepared by reaction of *o*-phenylenediamine with either homophthalic anhydride or, in two steps, with homophthalic acid followed by cyclization with acetic anhydride (66JOC1498).

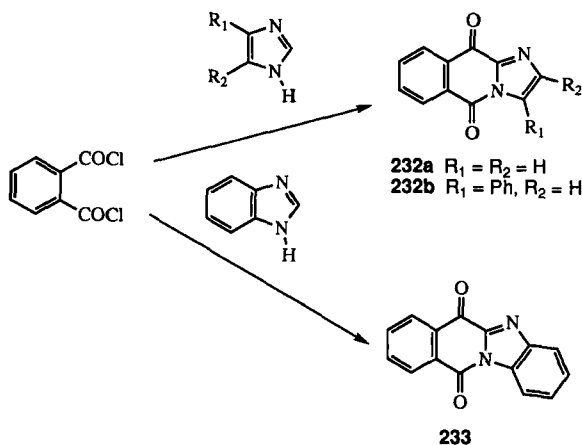
d. *Tetrazolo[1,5-b]isoquinoline-5,10-diones*. Thermal decomposition of 2,2-diazo-1,3-indanedione **237** provided high yield of the tricyclic



a	$R_1 = \text{Me}, R_2 = \text{Pr}, R_3 = \text{H}$	31 %
b	$R_1 = \text{Me}, R_2 = R_3 = \text{Ph}$	51 %
c	$R_1 = R_2 = R_3 = \text{Ph}$	41 %



SCHEME 55

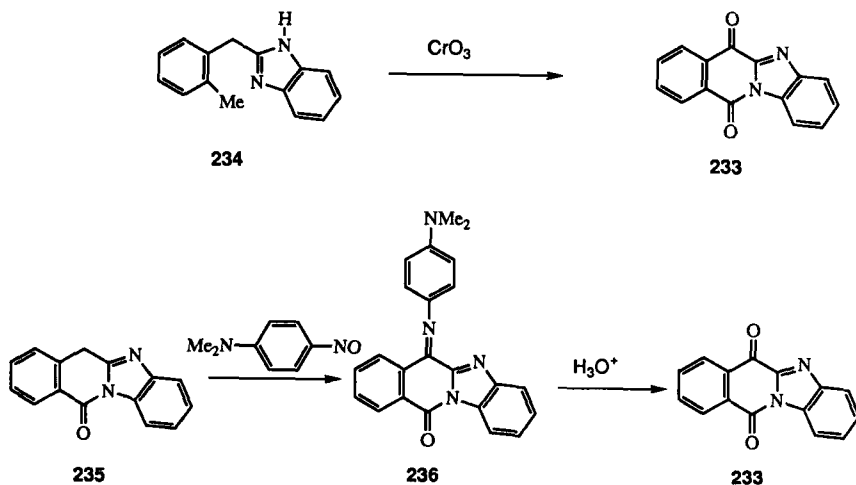


SCHEME 56

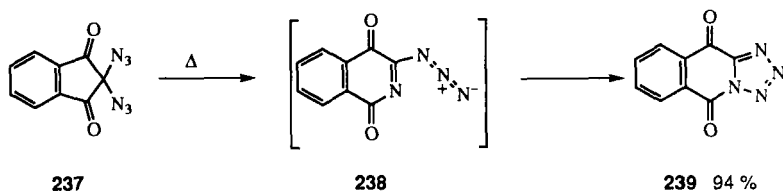
compound **239** (Scheme 58). Due to the analogy with thermal cyclization of various 2-azido-1,3-indanediones (see Scheme 12), the intermediacy of azoquinone **238** can be inferred (71TL1621).

2. Reactions

a. *Pyrrolo[1,2-*b*]isoquinoline-5,10-diones*. The most obvious reaction of pyrrolo[1,2-*b*]isoquinoline-5,10-diones is facile ring opening by aqueous



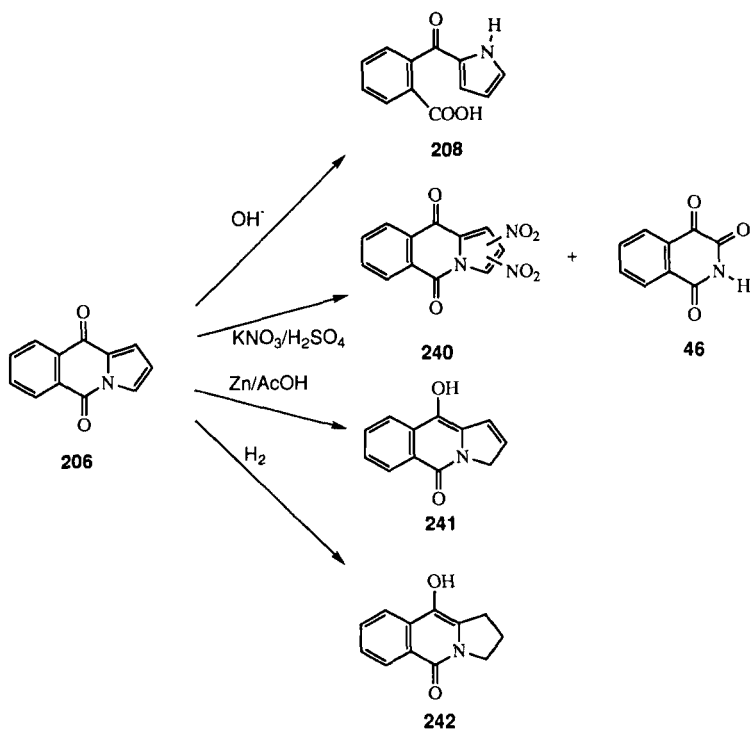
SCHEME 57



SCHEME 58

alkali, e.g., compound **206** to yield acid **208**. Interestingly, compound **206** does not react with hydrazine.

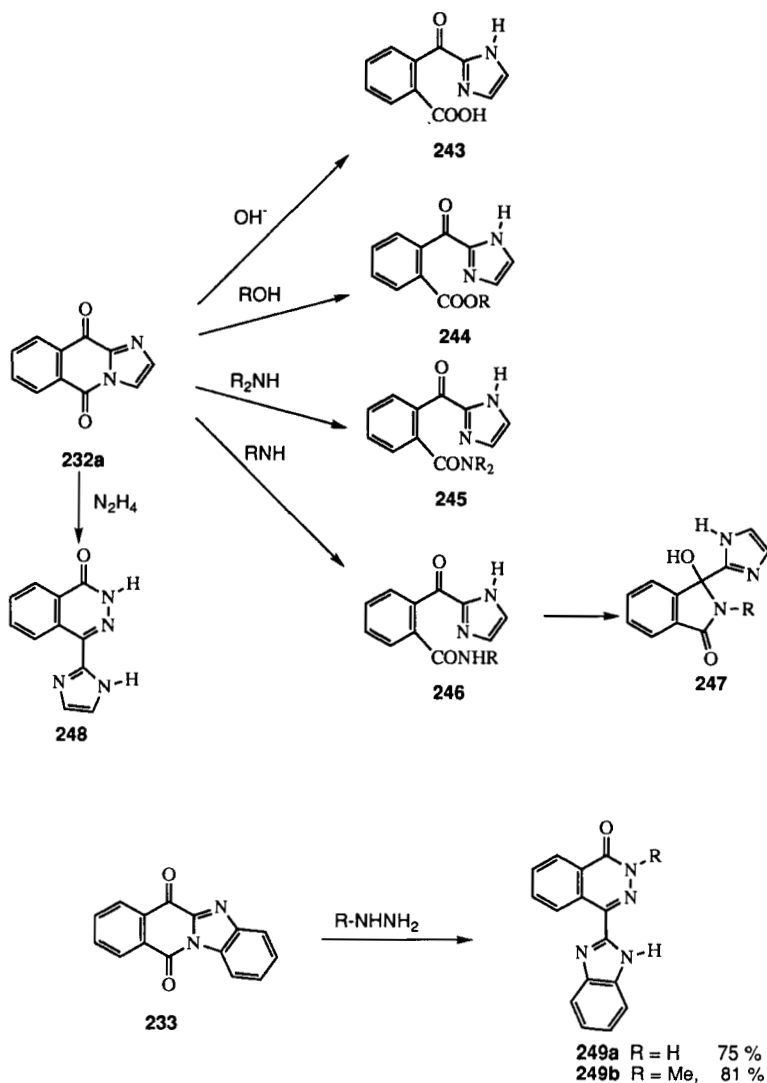
Nitration of **206** with a mixture of potassium nitrate and sulfuric acid yielded a mixture of dinitro derivative **240** and oxidation product **46**. Heating **206** with sodium borohydride led to hydrolysis to **208** rather than to any reduction product. On the other hand, reduction with zinc in cold acetic acid provided dihydro derivative **241**, whereas catalytic hydrogenation over palladium on carbon provided tetrahydro derivative **242** (Scheme 59) [90JCS(P1)1463].



SCHEME 59

b. *Pyrazolo[1,5-a]pyridine-4,7-diones*. No reactions of these compounds have been reported.

c. *Imidazo[1,2-b]isoquinoline-5,10-diones*. These compounds seem to be more reactive toward various nucleophiles than the corresponding pyrrolo[1,2-b]isoquinoline-5,10-diones (Scheme 60). Compound **232a** re-

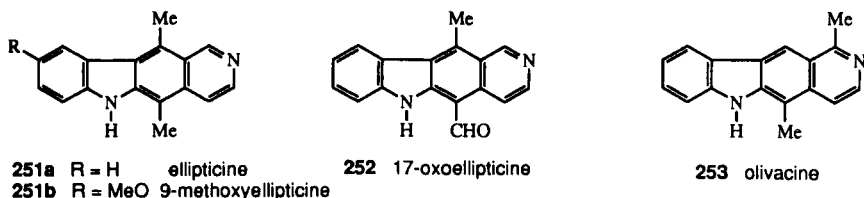


SCHEME 60

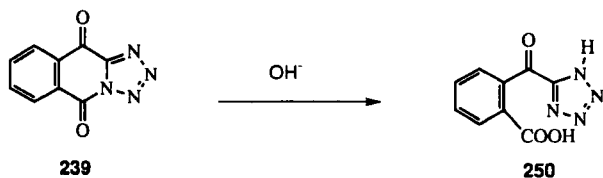
acts not only with alkaline aqueous hydroxides, but also with alcohols and amines to provide corresponding derivatives **243**–**246** in good yields (76JOC836; 80KGS335). Amides **246** having relatively small alkyl or aryl substituents, e.g., H, Me, Et, Pr, *i*-Pr, Ph, readily cyclized on protonation to provide **247** (80KGS335). Hydrazine and alkylhydrazines react with compounds **232a** and **233** to provide phthalazone derivatives **248** and **249**, respectively (76JOC836).

d. *Tetrazolo[1,5-b]isoquinoline-5,10-diones*. The only known reaction of this class of compounds is alkaline hydrolysis of **239** to **250** (Scheme 61) (75MI1).

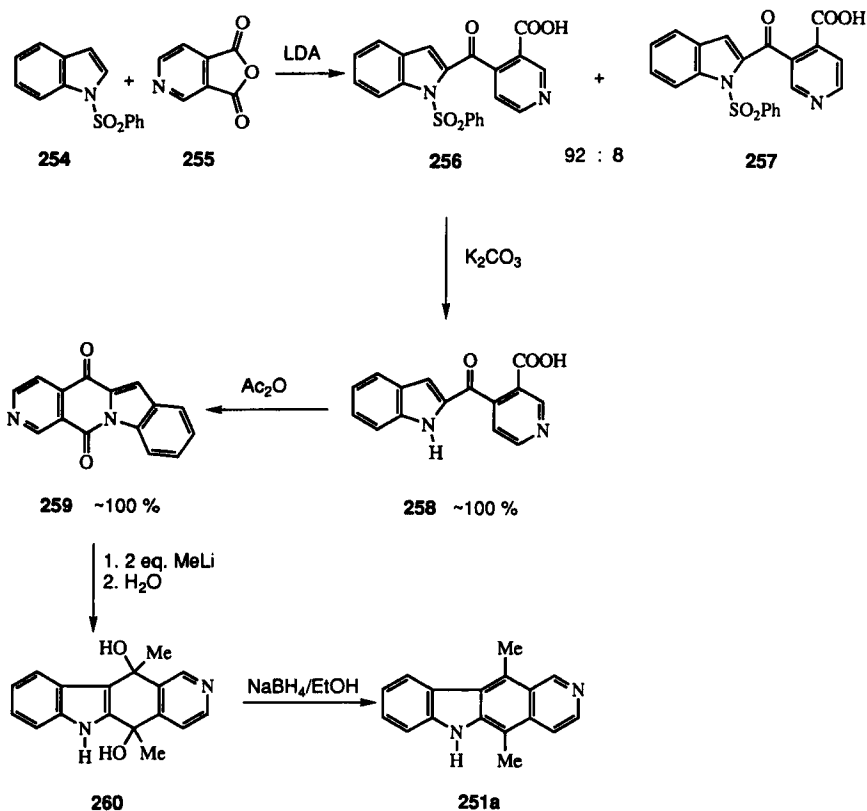
e. *Miscellaneous Applications*. Ellipticine **251a**, 9-methoxyellipticine **251b**, 17-oxoellipticine **252**, olivacine **253**, and some of their synthetic analogs are promising anticancer drugs, and therefore a convenient and versatile method for their synthesis is crucial both for their pro-



duction and for investigation of their new derivatives. Gribble with co-workers and others used various aza analogs of **223** as intermediates in the synthesis of ellipticine and its derivatives (82JOC2810; 83JOC2690, 83TL3831; 85JOC5451; 89JOC3264; 90TL5845; 91MI1; 92H1613, 92JOC 5891). Scheme 62 depicts the synthesis of ellipticine starting from *N*-benzenesulfonylindole, which provided ellipticine in 54% yield from indole. The fact that ketone carbonyl in **259** is more reactive toward nucleophilic addition than the lactam carbonyl group can be used for sequential treatment of this compound with different nucleophiles (Scheme 63) (83TL3831; 92JOC5891). For example, sequential treatment with vinylolith-

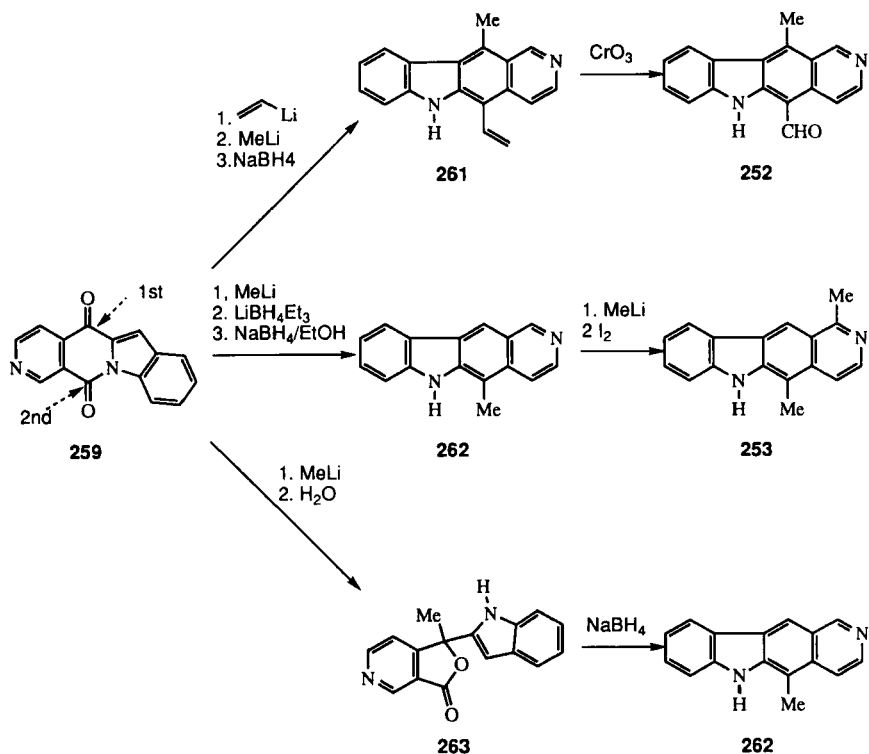


SCHEME 61



SCHEME 62

ium and methyllithium provided **261**, which on oxidation with chromium trioxide afforded 17-oxoellipticine **252** (91MI1; 92JOC5891). Similar sequential treatment of **259** with methyllithium and lithium triethylborohydride (Superhydride) provided after reduction of the intermediate diol 11-desmethoxyellipticine **262**, which can be easily converted into olivacine **253**. Modi *et al.* used trimethylsilyl chloride instead of Superhydride and noted good yields of 11-desmethoxyellipticine **262** (90TL5845). When compound **259** was treated with one equivalent of methyllithium and subsequently quenched with water, lactone **263** was obtained in 65% yield. This compound when reduced with sodium borohydride again afforded 11-desmethoxyellipticine **262** (90TL5845). Several other modifications of this procedure, which are beyond the scope of this review, were summarized in an account published by Gribble (91MI1).



SCHEME 63

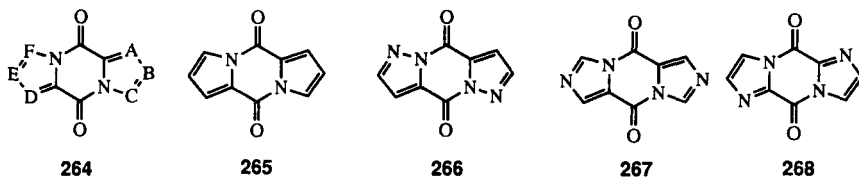
3. Spectroscopic Properties

Although these compounds are generally stable, no thorough investigation of their spectroscopic properties has been reported. Spectral characteristics used for the identification of these compounds are usually not very useful. The most general results are obviously in IR spectroscopy. These compounds have two strong bands in the carbonyl region, usually at about $1650\text{--}1675$ and $1690\text{--}1715\text{ cm}^{-1}$ (58JCS1091; 76JOC836; 82JOC2810; 93H1287).

C. AZAQUINONES CONTAINING TWO BRIDGEHEAD NITROGEN ATOMS

Formally there are several possible two-bridgehead nitrogen atoms containing structures derived from **192**–**194**. Compounds of general formula

264 have been described and most of them are symmetrical structures, as shown in structures **265–268**.



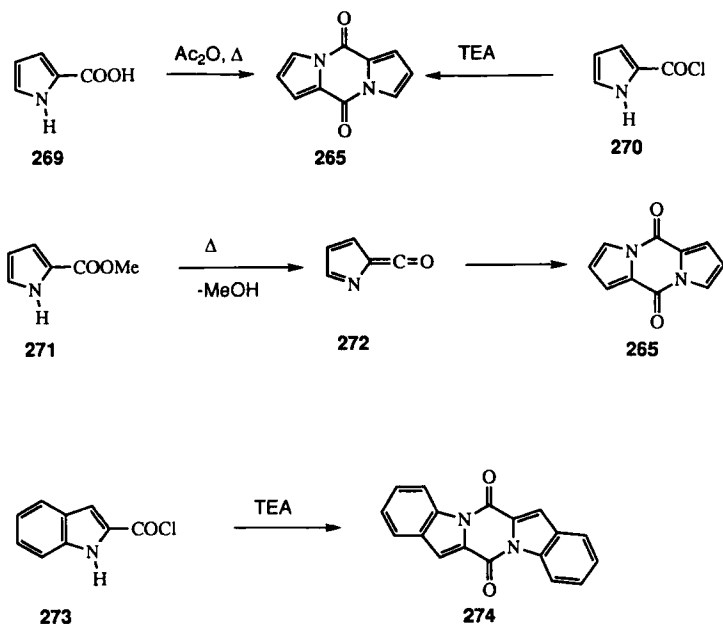
A,B,C,D,E,F = CH or N

1. Synthesis

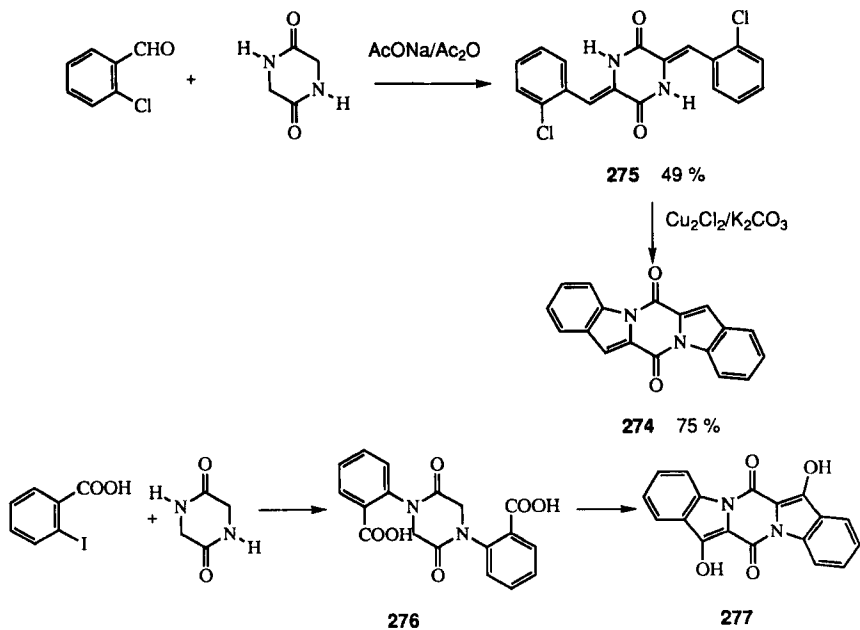
a. *Dipyrrolo[1,2-a:1',2'-a]pyrazine-5,10-diones*. The simplest example of diazaquinones having two bridgehead nitrogen atoms is dipyrrolo[1,2-a:1',2'-a]pyridazine-5,10-dione **265**, called in the older literature pyrocoll. This compound is also present in cigarette smoke, probably as a product of proline pyrolysis (60MI1). The compound can be prepared by dehydration of pyrrole-2-carboxylic acid **269** by heating with acetic anhydride (60MI1). The same product is also obtained under milder conditions by a treatment of acyl chloride **270** with triethylamine (76JOC3050). Flash vacuum pyrolysis of pyrrole-2-carboxylic acid or its methyl ester **271** provided 1-azafulven-6-one **272**, which undergoes dimerization to the energetically favored **265** (82CC360). Similar benzo analog **274** was also prepared from indolecarbonyl chloride **273** by a treatment with triethylamine (Scheme 64) (76JOC3050). The same product was also prepared from 2-chlorobenzaldehyde and dioxopiperazine (77JOC948). These compounds when treated with sodium acetate in acetic anhydride condensed to provide intermediate **275**, which was cyclized with cuprous chloride and potassium carbonate in diglyme to afford **276** (Scheme 65). Arylation of diketopiperazine with 2-iodobenzoic acid afforded acid **276**, which can be cyclized to dihydroxy derivative **277** either directly or via its dimethyl ester (Scheme 65) (77JOC948).

A different approach was used by Schaefer and Gewald for preparation of dimethyl derivative **279** (Scheme 66). They treated acetophenone derivative **278** with sodium methoxide in DMF and obtained **279** in high yield. The corresponding desmethyl amino derivative was obtained similarly from 2-chloroacetamido benzonitrile (87JPR745).

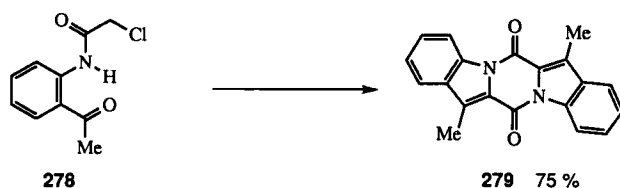
b. *Dipyrzolo[1,5-a,1',5'-d]pyrazine-4,9-diones*. The simplest member of this group, i.e., compound **266**, and its derivatives, can be prepared from corresponding pyrazole-3-carboxylic acids **280** by a treatment with



SCHEME 64



SCHEME 65

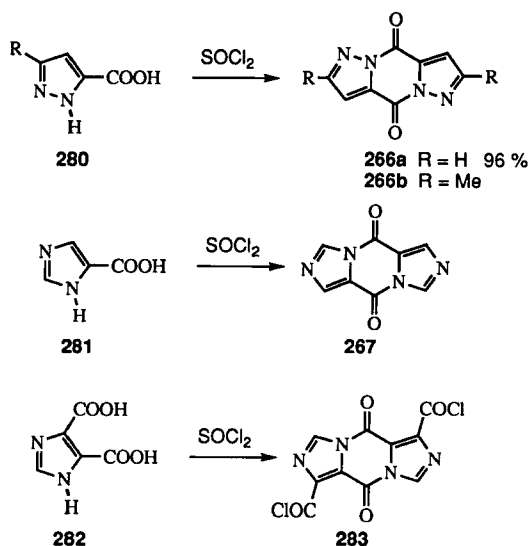


SCHEME 66

thionyl chloride (45G121; 47G19; 84MI1; 85JPS1013; 92CB701). No other method of preparation of these compounds has been reported.

c. *Diimidazo[1,5-a:1',5'-d]pyrazine-5,10-diones and Diimidazo[1,2-a:1',2'-d]pyrazine-5,10-diones.* Diimidazo[1,5-a:1',5'-d]pyrazine-5,10-dione **267** can be prepared by refluxing the corresponding acid **281** with thionyl chloride (74JMC1168), although an earlier study reported unchanged starting material (16JCS186). The dinitro derivative of **267** can be prepared from 5-nitroimidazole-4-carboxylic acid by the same procedure (87JMC357; 90JMC1393). Dicarboxylic acid **282** when treated with thionyl chloride or phosphorus pentachloride provided bis acylchloride **283** (Scheme 67) (84SC251).

Dicarboxylic acid **282** on reflux with acetic anhydride is reported to cyclize and decarboxylate to **267** (75S162). Acetic anhydride can be used



SCHEME 67

also with monocarboxylic acids, as demonstrated by the synthesis of **285** (Scheme 68) (64JOC3707). Imidazole-2-carboxylic acids **286** treated with thionyl chloride provided the corresponding diimidazo[1,2-*a*,1',2'-*d*]pyrazine-5,10-diones **267** (59CB550). A benzo analog of diimidazo[1,5-*a*,1',5'-*d*]pyrazine-5,10-dione **289** was prepared analogously from benzimidazol-2-carboxylic acid **288** (Scheme 69) [79IJC(B)464].

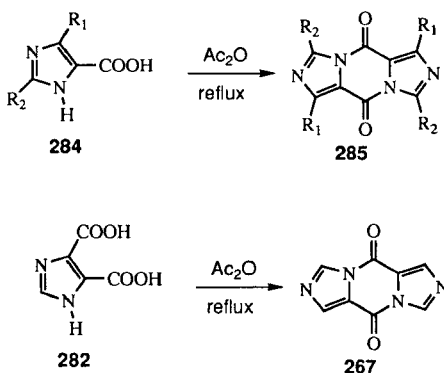
Tetrachloro derivative **287b** was also prepared in 60% yield from cyanogen and oxalyl chloride by prolonged heating in the presence of a catalytic amount of hydrochloric acid and quaternary ammonium chloride (Scheme 70) [88AG(E)1372].

Flash vacuum pyrolysis of methyl imidazol-2-yl carboxylate **290** at 750°C gave 20% yield of **268** via the corresponding ketene **291**. Similar pyrolysis of methyl imidazol-1-yl carboxylate **292** gave 20% of a 1 : 1 : 2 mixture of compounds **267**, **268**, and **296**. This fact can be rationalized by the pathway depicted in Scheme 71. Ketenes **291** and **295** may be intermediates formed from **293** and **294**, respectively. They are products of rearrangement of **292**. Similar pyrolysis of 4-imidazole carboxylic acid anilide performed at 800°C gave **267** in 20% yield (86JOC306).

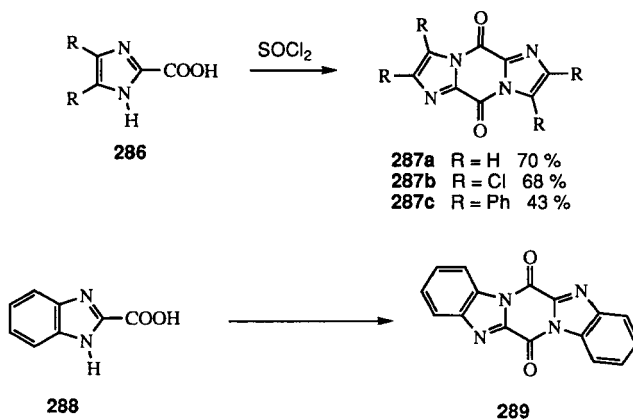
Compound **297** was formed in low yield during anodic oxidation of the corresponding diketopiperazine in acetonitrile (Scheme 72) (70TL3303).

2. Reactions

a. *Dipyrrolo*[1,2-*a*:1',2'-*a*]pyrazine-5,10-diones. The most obvious reaction of azaquinones containing two bridgehead nitrogen atoms is their reaction with nucleophiles. For example, their reaction with water provides the corresponding acids.



SCHEME 68



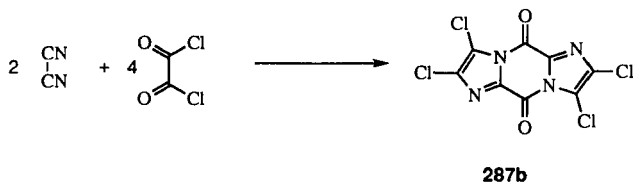
SCHEME 69

Dihydroxy derivative **277** when treated with sulfur monochloride provided in 65% yield sulfur-bridged diketopiperazine structure **298** (Scheme 73) (77JOC948).

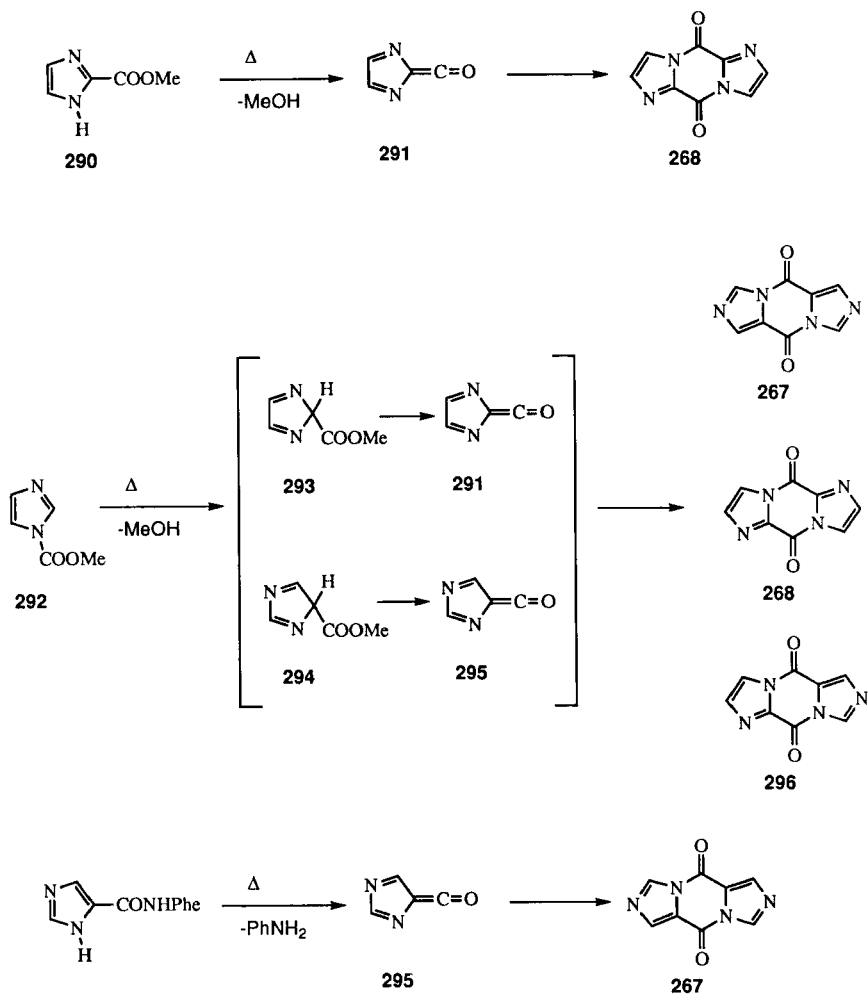
b. *Dipyrazolo[1,5-a:1',5'-d]pyrazine-4,9-diones*. Dipyrazolo[1,5-a:1',5'-d]pyrazine-4,9-diones show a reasonable reactivity toward amines, including relatively poor nucleophiles such as aniline derivatives. For example, **266b** when treated with a wide range of aniline derivatives provided anilides **299** in yields of about 65–85% (85JPS1013). Piperazides **300** (75MI2) and hydrazides **301** were prepared in a similar manner (Scheme 74) (84MI1).

Reaction of **266a** with suitable methyl alkyl amines having an asymmetric center at the neighboring carbon atom provided optically active amides **302**, which after reduction with LAH gave optically active pyrazolylmethyamines **303** (92CB701).

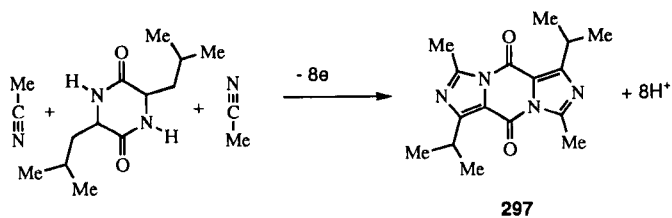
c. *Diimidazo[1,5-a:1',5'-d]pyrazine-5,10-diones and Diimidazo[1,2-a:1',2'-d]pyrazine-5,10-diones*. Diimidazo[1,5-a:1',5'-d]pyrazine-5,10-dione **267** reacts with a number of nucleophiles, including alcohols, amines,



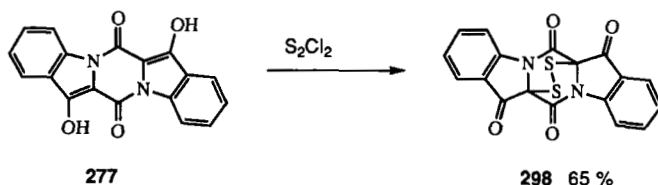
SCHEME 70



SCHEME 71



SCHEME 72

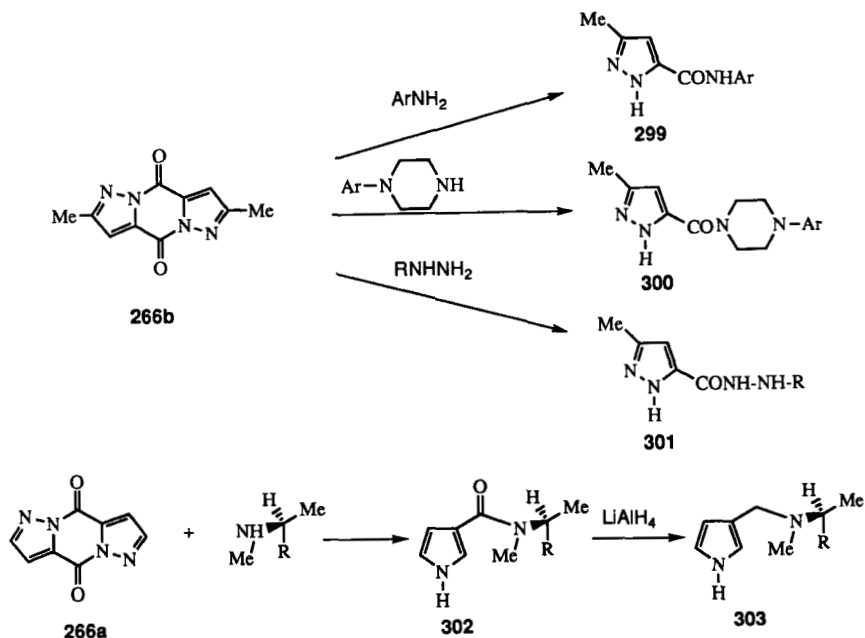


SCHEME 73

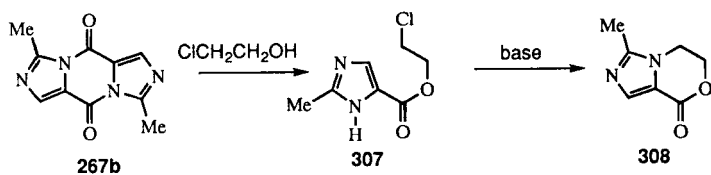
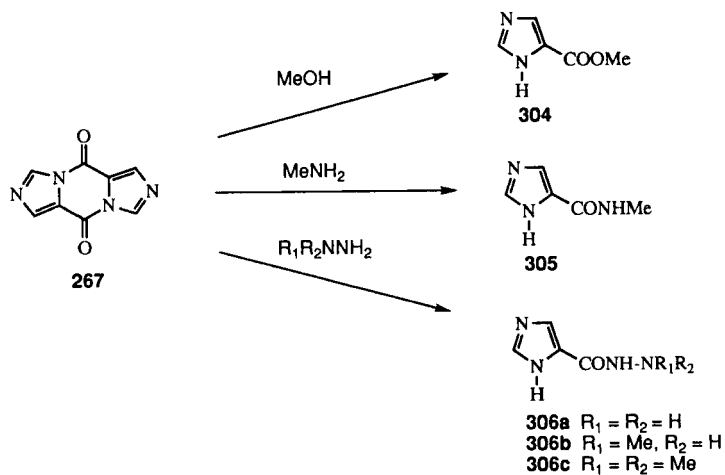
hydrazine, methylhydrazine, and *N,N*-dimethylhydrazine (74JMC1168; 75S162; 86MI1; 87JMC357; 90JMC1393) (Scheme 75). The reaction with *N,N*-dimethylhydrazine is of particular interest since hydrazide **306c** and similar disubstituted hydrazides cannot be prepared by reaction of hydrazine with the corresponding esters (74JHC351).

A similar reaction with ethylenechlorhydrin gave intermediate ester **307**, which under alkaline conditions cyclized to lactone **308** (64JOC3707).

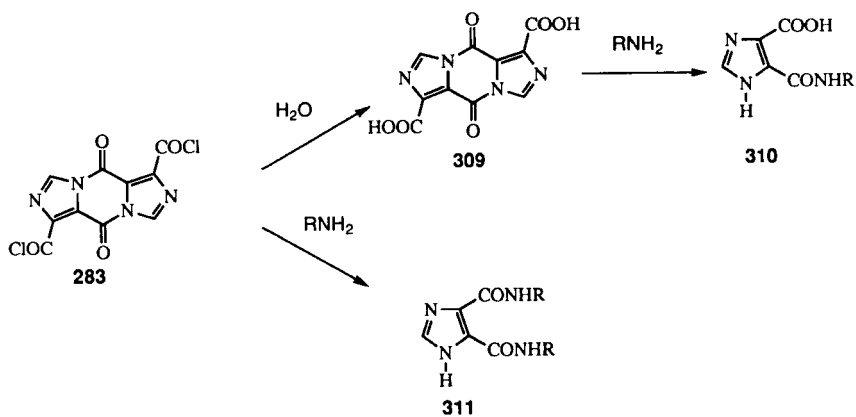
Bis-acylchloride **283** can be hydrolyzed under mild conditions to the corresponding dicarboxylic acid **309**, which when treated with amines gave monoamides **310**. The corresponding imidazolediamides **311** were prepared when the bis-acylchloride was directly treated with the amines (Scheme 76) (84SC251).



SCHEME 74



SCHEME 75



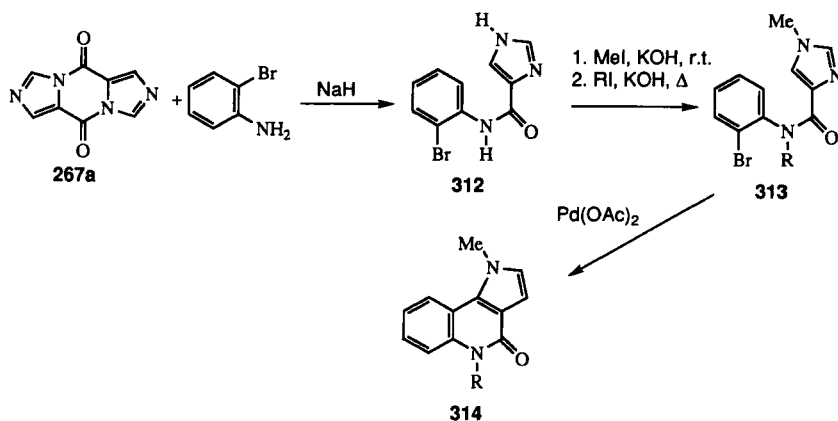
SCHEME 76

Kuroda and Suzuki used reaction of **267a** with 2-bromoaniline leading to anilide **312** as the first step of their sequence in the preparation of 1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones (Scheme 77) (91TL6915). Reaction of **267a** with amines usually does not require any catalyst and/or base, but in this case use of sodium hydride was reported. The anilide **312** was sequentially alkylated, first with methyl iodide in ethanol with potassium hydroxide at room temperature and then with different alkyl iodides in acetone at reflux to provide intermediate **313**. This compound was then cyclized via palladium catalyzed reaction leading to product **314**. This reaction provides a new entry to 1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones that are of current interest as antiasthmatic agents.

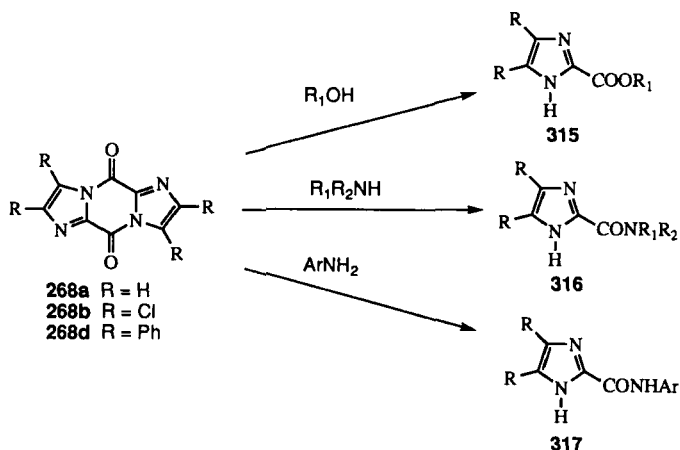
Diimidazo[1,2-*a*:1',2'-*d*]pyrazine-5,10-diones, in a manner similar to that of other azaquinones containing two bridgehead nitrogen atoms as discussed earlier, react with a wide variety of nucleophiles to provide the corresponding derivatives of imidazole-2-carboxylic acid (Scheme 78). Reaction with alcohols, ammonia, and primary and secondary amines gave nearly quantitative yields of products **315**–**317** [59CB550; 80JHC409; 88AG(E)1372]. The reaction with aniline derivatives is notable and affords high yields of **317**.

3. Spectroscopic Properties

Although these compounds are generally stable, no thorough investigation of their spectroscopic properties has been reported. Spectral characteristics used for identification are usually not very useful. The most general results are obvious in IR spectroscopy. These compounds usually



SCHEME 77



SCHEME 78

have one strong band in carbonyl region, at about $1720\text{--}1750\text{ cm}^{-1}$ [80JHC409; 88AG(E)1372; 92CB701].

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Condensed 1,2,4-Triazines: II. Fused to Heterocycles with Six- and Seven-Membered Rings and Fused to Two Heterocyclic Rings

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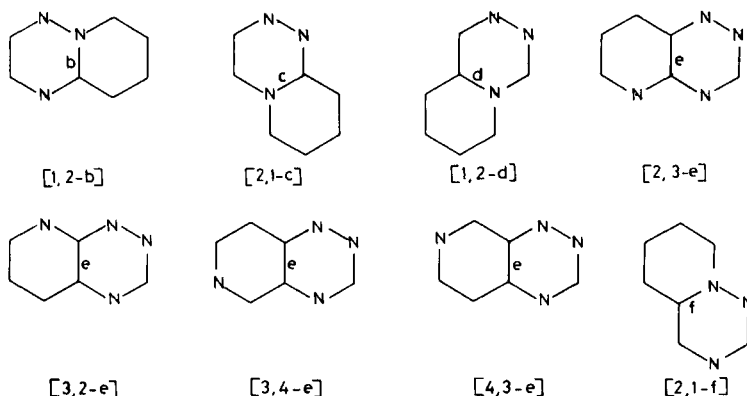
I. Introduction

A review of condensed 1,2,4-triazines with heterocycles having three- to five-membered rings has been recently published in this series (94AHC39). The present review deals with condensed ring systems of 1,2,4-triazines with six- and seven-membered heterocycles as well as condensed ring systems with the triazine in the center. The review contains literature from 1974 to 1992 (*Chemical Abstracts*, Vol. 116). Previous literature was reported earlier [78HC(33)749]. The same strategy used for the arrangement of the previous part on this subject (94AHC39) is used here. The arrangement follows the order of increasing number of heteroatoms in the fused ring and each is followed in turn by a heterocycle fused to a benzene ring. In the case of a trivial name, the compound will be given under a separate subheading. Each fused ring system is arranged according to the order of fusion on the triazine ring.

II. Pyrido[1,2,4]triazines

A. PYRIDO[*x,y-z*][1,2,4]TRIAZINES

There are eight theoretically possible pyridotriazines. Four of them possess a bridgehead nitrogen with faces *b*, *c*, *d*, and *f* common to the triazine ring. The other four isomers all have face *e* in common. Their UV spectral properties are dependent on the position of the pyrido *N*-atom (78ACH61). They are represented by the following general formulas.

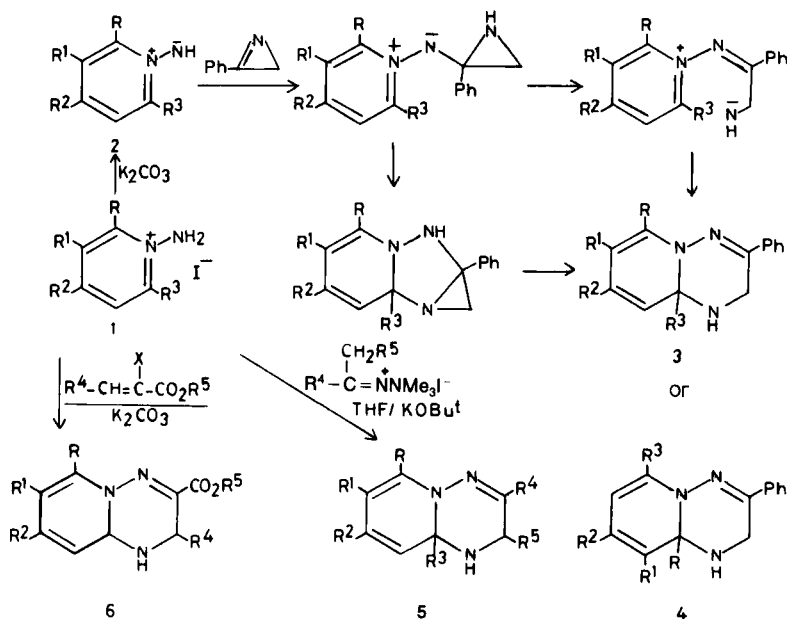


SCHEME 1

1. Pyrido[1,2-*b*][1,2,4]triazines

1-Aminopyridinium salts are attractive starting materials for the construction of the skeleton of such heterocycles. Thus, pyridinium *N*-imine hydriodides **1** reacted with 2-phenylazirine in the presence of the K_2CO_3 to give the corresponding 3-phenyl-1,9*a*-dihydro-2*H*-pyrido[1,2-*b*][1,2,4]triazines **3** (75JOC544). When **1** has various substituents on the ring, its reaction with phenylazirine gave (76JOC2739) the pyridotriazines **3** and/or **4**. The reaction proceeds via initial electrophilic addition of 2*H*-azirine to the *N*-imines **2**, followed by homo 1,5-dipolar cyclization ($\pi^{4s} + \pi^{2s}$) of the resulting *N*-(2-aziridinyl)iminopyridinium ylide or by cyclization of a 1,6-dipolar species resulting from it to give **3**. An alternative route to **3** involves initial 1,3-dipolar cycloaddition of the *N*-imines with the azirine to give the respective tricyclic adduct, followed by 1,3-shift of the amino hydrogen.

The Neber reaction of **1** with the hydrazone salts in tetrahydrofuran containing potassium *tert*-butoxide gave **5** (77JOC2514), where azirines



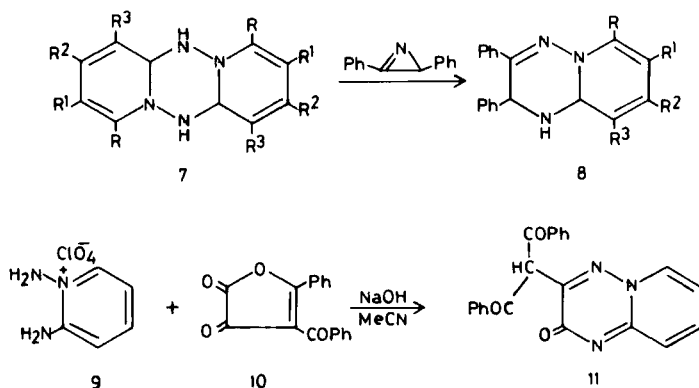
SCHEME 2

were generated *in situ* but treated without isolation. On the other hand, **1** could be reacted with α -halogeno unsaturated esters in the presence of potassium carbonate to give (75MI3) the pyrido[1,2-*b*][1,2,4]triazines **6**, presumably via the formation of an azirine or aziridine intermediates from the unsaturated acid.

N-Imine dimers **7** reacted with 2,3-diphenylazirine to give (76JOC2739) the corresponding pyridotriazines **8**. Pyridinium *N*-imine was useful as a trapping agent for transient azirine.

When the diamino salt **9** was treated with the 2,3-furandione **10**, it gave the pyrido[1,2-*b*][1,2,4]triazinone **11**, whose reaction with base gave the respective monobenzoyl derivative (89CB1935). Cyclocondensation of 1,6-diaminopyridines **12** with diacetyl gave [73KGS1266; 90JCR(S)186] pyridol[1,2-*b*][1,2,4]triazines **13**. On the other hand, reaction with benzil was unsuccessful.

The reaction of 1-(2-pyridyl)-3,5-dinitro-2-pyridone **14** with ethyl sodio acetoacetate or diethyl sodio acetone-dicarboxylate gave a mixture of *N*-(2-pyridyl)nitroacetamide **15**, phenol derivatives **16**, and a low yield of 2-oxo-2,5-dihydropyrido[1,2-*b*][1,2,4]triazine 4-oxide **17** (79TL1393). The mechanism of the reaction is shown in Scheme 5.



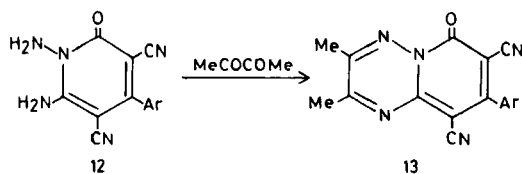
SCHEME 3

2. *Pyrido[2,1-c][1,2,4]triazines*

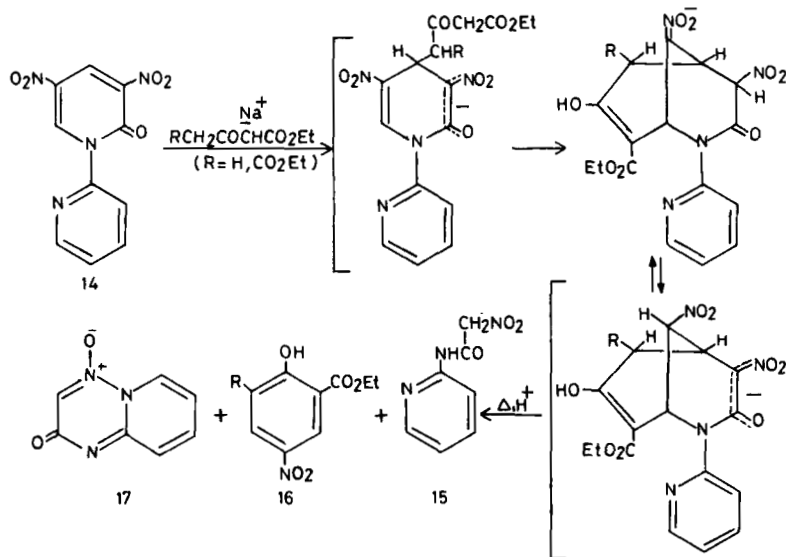
The partially hydrogenated pyridotriazine **19** was prepared (77AP588) by the dehydrogenation of **18**. Alternatively, it was prepared by the reaction of ethyl- α -chlorophenylacetate with the respective lactam followed by reaction with hydrazine.

The pyridotriazines **21** and **22** were obtained (84JHC1765) by the cyclization of the 2-chlorolpropargyl pyridinium bromide **20** with methylhydrazine or 1,2-dimethylhydrazine, respectively. On the other hand, when hydrazine or acetylhydrazine were used in the reaction, imidazopyridinium salts were formed.

The indolo analogue **25** was prepared (86AP659) by alkylation of 9-methyl-3,4-dihydro- β -carboline **23** with phenacyl bromide followed by perchloric acid to give **24**. Reaction of **24** with hydrazine hydrate gave triazinopyridindole **25**, which underwent 1,12*b*-dehydrogenation with Hg(II)-EDTA (86AP659).



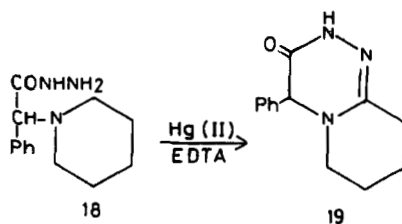
SCHEME 4



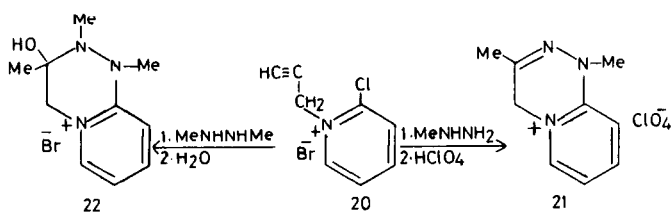
SCHEME 5

3. *Pyrido[1,2-d][1,2,4]triazines*

The reaction of 2-acetylpyridine **26** with methylhydrazine gave the corresponding hydrazone **27**, which was condensed with carbon disulfide to give 3,5-dimethyl-5-(2-pyridyl)-1,3,4-thiadiazolidine-2-thione **28**. Its alkylation with iodomethane gave **29**, whose reaction with a dialkylamine gave pyrido[1,2-*d*][1,2,4]triazin-4-thiones **30** (80JOC4372). In solution, **30A** is orange, whereas crystals of the compound are deep purple. This suggests that the predominant form in solution is the cyclized form and the purple coloration of the solid may be explained by conversion to a dipolar form with greater extended conjugation, as in **30B**.



SCHEME 6



SCHEME 7

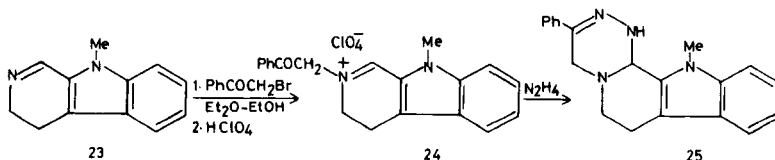
4. Pyrido[2,3-*e*][1,2,4]triazines

This ring system was prepared (80MI2) by the cyclocondensation of **31** with potassium *tert*-butoxide and the product was brominated and treated with triethylamine to give **32**. Derivatives were prepared by reaction of **32** with amines to yield **33**, which were converted to the respective 7-carboxylic acid that exhibited bactericidal activity.

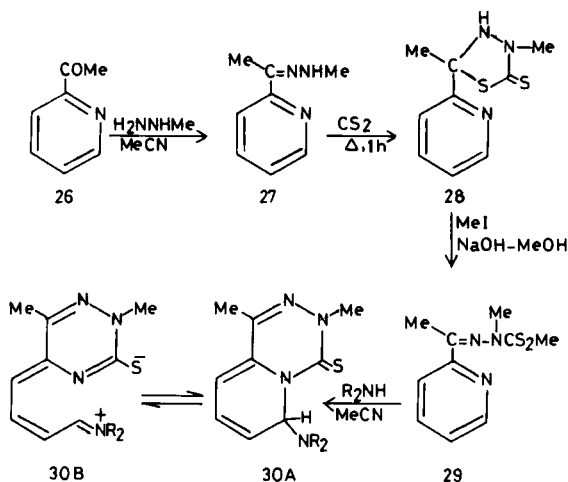
The parent heterocycle of pyrido[2,3-*e*][1,2,4]triazine and its phenyl derivative **39** were prepared (89JHC475) by cyclization with polyphosphoric acid of 3-acylhydrazino-2-aminopyridines **36**, obtained by reduction of the corresponding 3-acylhydrazino-2-nitropyridines **35**. Compounds **35** were obtained from 3-fluoro-2-nitropyridine **34** either by reaction with benzoylhydrazine or by reaction with hydrazine and subsequent formylation of the initially formed 3-hydrazino-2-nitropyridine **38**. Attempts to prepare **38** from 3-chloro-2-nitropyridine gave 2-hydrazino-3-chloropyridine **37**. These results could be explained by semiempirical calculations (CNDO and MNDO calculations).

3-Methylthiopyrido[2,3-*e*][1,2,4]triazine **41** was prepared (76KGS1140) by cyclization of 2-amino-3-hydrazinopyridine **40** with carbon disulfide followed by methylation. Oxidation of **41** with chlorine afforded the 3-methylsulfonopyridotriazine **42**. Heating **41** with morpholine or pyrrolidine gave **43**, whereas the reaction at 20°C gave **44**.

N-benylation of the sodium salt of 4*H*-pyrido[2,3-*e*][1,2,4]triazin-3-one 1-oxide **45** gave (82JHC497) the respective 4-*N*-benzyl derivative.



SCHEME 8



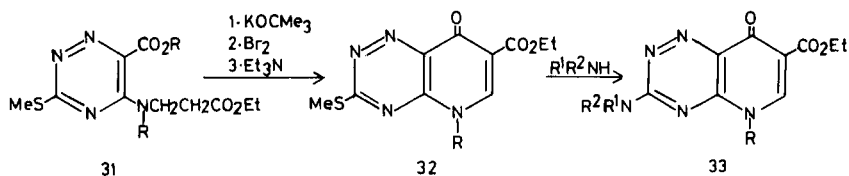
SCHEME 9

Similarly, treatment of the salt with 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide **46** gave 4-[2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl]-4*H*-pyrido[2,3-*e*][1,2,4]triazin-3-one 1-oxide **47**. Antileukemia tests for the 4-alkyl derivatives showed no activity.

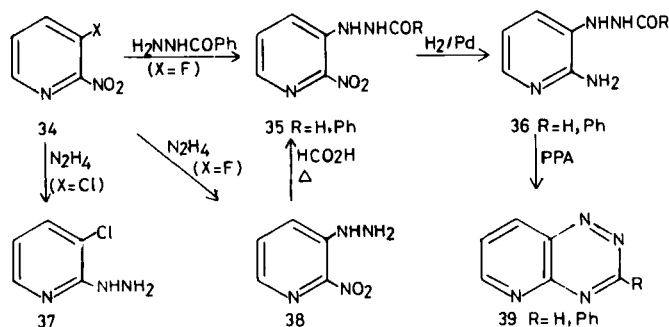
Optical recording material with Laser-writing and Laser-reading capabilities consists of the metal complex **48** [91JAP(K)0313384].

5. Pyrido[3,2-*e*][1,2,4]triazines

Bishler's benzo[1,2,4]triazine synthesis was extended to the synthesis of pyrido[3,2-*e*][1,2,4]triazines **54** [75BEP832791; 75MIP1; 76ACH301; 76CR(C)487; 76MI2] starting with 2-chloro-3-nitropyridine **49** or the respective fluoro analogue and reacting it with acylhydrazines to give the hydrazides **50**, which also resulted by acylating 2-hydrazino-3-nitropyridine **51**. Catalytic reduction of the hydrazides **50** and cyclization of the resulting amino derivative **52** gave **53**, whose oxidation with potassium



SCHEME 10



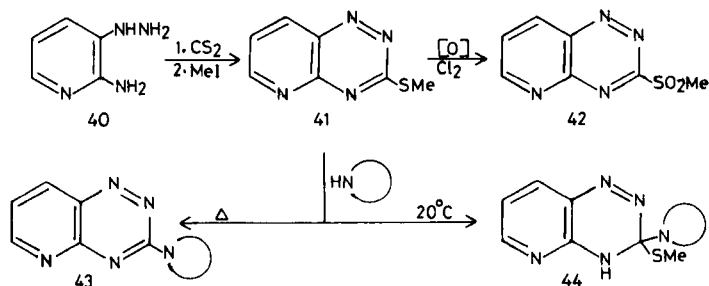
SCHEME 11

ferricyanide at pH 10 or with air gave **54**. Cyclization of the hydrazone **55** with acid gave **53** (77BRP1492073). Compounds **53** and **54** were prepared as antibacterial and anti-inflammatory agents. Mono- and di-*N*-acyl derivatives of **53** were prepared (80NEP8002481, 80NEP8003036) and tested for their anti-inflammatory and analgesic activities as well as spontaneous motor activity.

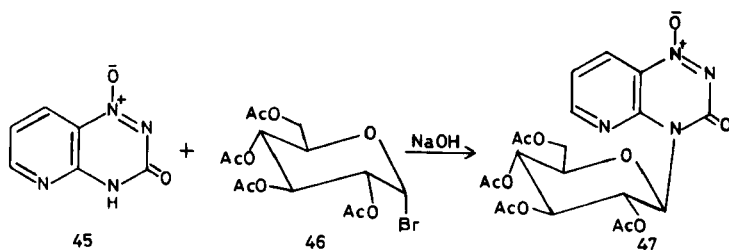
Homolytic annulation of Schiff bases **56**, via an intermolecular free-radical addition of its arylimidoyl radicals **57** to the azo group of diethyl azodicarboxylate (89CC757) in the presence of diisopropylperoxy dicarbonate (DPDC), gave 1,2-diethoxycarbonyl pyrido[1,2,4]triazines **60** via **58** and **59**. No trace of the other isomer could be detected.

The catalytic hydrogenation of 3-phenylpyrido[3,2-*e*][1,2,4]triazine **54** ($R^1 = Ph$) gave the corresponding 1,4-dihydro derivative **61**, whereas its reduction with $LiAlH_4$ afforded the 5,6,7,8-tetrahydro derivative **62**. Also, electrochemical reduction of **54** ($R^1 = Ph$) in acetonitrile in the presence of phenol gave **61** (81JOC4754).

An optical recording material that is an analogue of **48** but with fusion of the pyrido[3,2-*e*][1,2,4]triazine type was also reported [91JAP(K)0313384].



SCHEME 12

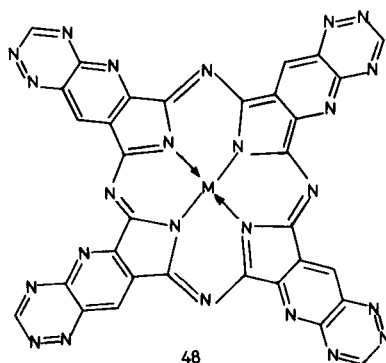


SCHEME 13

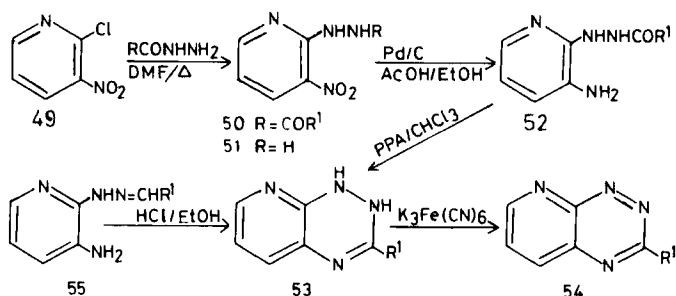
6. *Pyrido*[3,4-*e*][1,2,4]triazines

4-Chloro- and 4-alkoxy-3-nitropyridines are key starting materials for the synthesis of 3-substituted-1,2-dihydropyrido[3,4-*e*][1,2,4]triazines **67** [75BEP832792, 75MIP2; 76ACH285, 76CR(C)487, 76MI1; 79URP646912; 81URP888823]. 3-Fluoro-4-nitropyridine oxide could also be used [76CR(C)487]. Reaction of the 4-chloro derivative with acylhydrazines gave the hydrazides **64**, which could also be obtained by acylating 3-nitro-4-hydrazinopyridine **63**. Catalytic reduction of **64** followed by ring closure of the resulting amino derivative **66** gave the dihydropyridotriazines **67**, which on oxidation with potassium ferricyanide gave **68**.

The hydrochloride of 3-amino-4-hydrazinopyridine **65** was prepared by reaction of the 4-chloro-3-nitropyridine derivative with ethoxycarbonylhydrazine in phenol to give the hydrochloride of ethyl 3-(3-nitro-4-pyridyl)carbazate **64** ($R^2 = \text{OEt}$), which on successive heating in concentrated hydrochloric acid and hydrogenation over Pd/C gave **65**. Its reaction with phenylacetic acid or with phenoxyacetic acid gave the hydrochloride



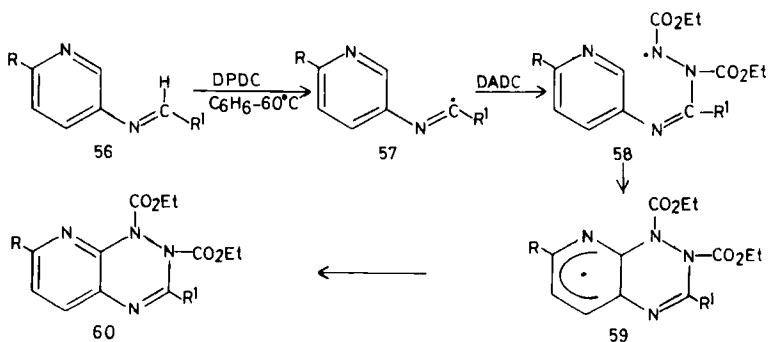
SCHEME 14



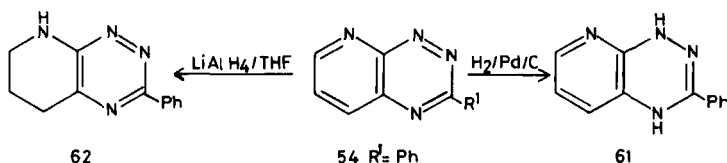
SCHEME 15

of **67**, which was oxidized with manganese dioxide to give **68** (75GEP2427377, 75GEP2427382). Attempts to cyclize the hydrochloride of **64** ($\text{R}^2 = \text{OEt}$) to this ring system failed (76JHC601). Antibacterial, anti-inflammatory, and antifungal activity of **68** were reported. Derivatives of **68** inhibited strains of *Candida*, *Aspergillus*, *Mucor*, and *Trichophyton* species. Some were more active than miconazole but less active than amphotericin (88ANY101; 89JMC2474).

Hydrogenation of 3-phenylpyrido[3,4-*e*][1,2,4]triazine **69** in the presence of Pd/C gave the 1,4-dihydro derivative **70**. Reduction of **69** by LiAlH_4 led to the unexpected formation of the tetrahydro derivative **71** in which both rings are partially reduced (81JOC4754). Electrochemical reduction of **69** in acetonitrile in the presence of acetic anhydride gave a mixture of 1,4-diacetyl-1,4-dihydro **72** and 1,2-diacetyl-1,2-dihydro derivatives **73**. Heating **70** with acetic anhydride gave **72**, which is also obtained by thermal isomerization of **73**. Derivatives of **70** had anti-inflammatory, analgesic, tranquilizing, antidepressant, and/or central nervous system-depressant activity (80GEP3006719).



SCHEME 16



SCHEME 17

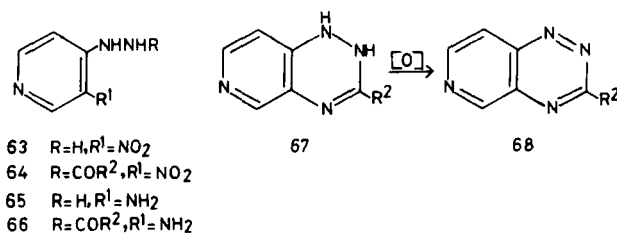
The thermal degradation of 3-(phenylmethyl)pyrido[3,4-*e*][1,2,4]triazine gave a large number of compounds, but only 3-(phenylmethyl)pyrido[3,4-*e*][1,2,4]triazin-5(6*H*)-one and 3-phenyl-1-(phenylmethyl)imidazo[3,4-*b*]pyrido[3,4-*e*][1,2,4]triazine were identified (82JHC1533).

7. Pyrido[4,3-*e*][1,2,4]triazines

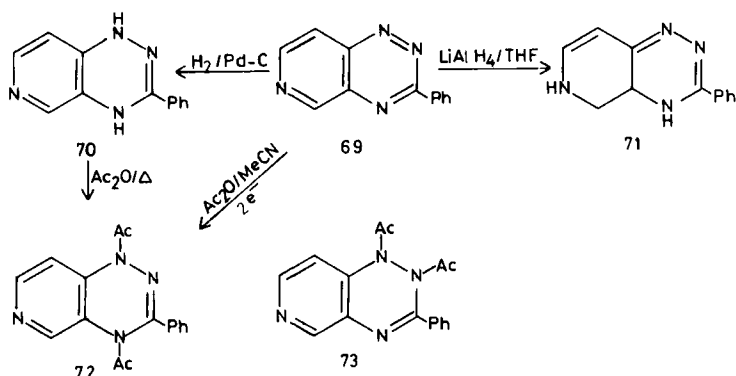
Pyridotriazine oxides **74** were prepared (76ACH405, 76MI6) in one step from the reaction of 4-chloro-3-nitropyridine and guanidine. Base-catalyzed rearrangement of **74** gave triazolopyridines **75**, and its oxidation gave the 1,4-dioxide, whose amino group could be replaced by amines with a simultaneous deoxygenation. Photolysis of 3-aminopyrido[4,3-*e*][1,2,4]triazine **77** or **74** in anhydrous methanol gave 3-[(methoxymethyl)amino]pyrido[4,3-*e*][1,2,4]triazine **76** and **77**, respectively (76ACH327, 76MI7). The structures and conformations of the diacetyl derivatives of the dihydropyridotriazine were studied (85CJC3210).

8. Pyrido[2,1-*f*][1,2,4]triazines

Most of the synthetic approaches toward this ring system utilize *N*-amino pyridinium salts functionalized at the α -position with a carbonyl group. Thus, the amination of 2-(1,3-dioxolan-2-yl)pyridine with tosylhydroxylamine gave **78**, whose reaction with urea in the presence of boron trifluoride-acetic acid gave **79**, which gave the thermally unstable



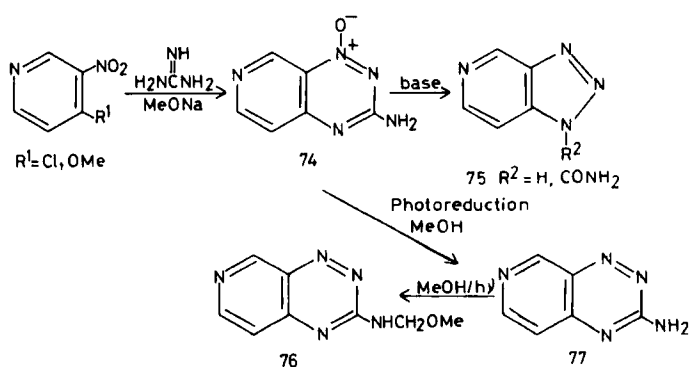
SCHEME 18



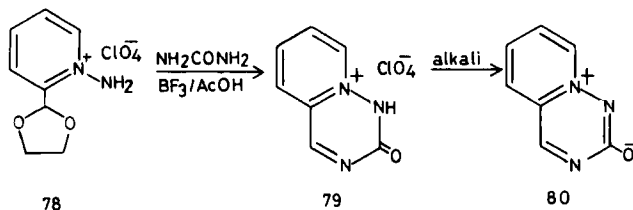
SCHEME 19

triazinium-3-olate **80** on treatment with alkali (86JHC375). The use of a protected aldehyde is necessary, as the amination of pyridine-2-aldehyde gave a multicomponent mixture.

Treatment of 2-benzoylpyridine **81** with *p*-toluene-sulfonamide gave 1-amino-2-benzoylpyridinium tosylate **82** ($X = \text{OTs}$), which was cyclized with formamide in the presence of triethylamine hydrobromide to give **83** (82FRP2486942). The reaction of the perchlorate **82** ($X = \text{ClO}_4$) with urea in polyphosphoric acid afforded 3-hydroxy-1-phenylpyrido[2,1-*f*][1,2,4]triazinium perchlorate **84**. Treatment of this salt with base led to the zwitterionic 1-phenylpyrido[2,1-*f*][1,2,4]triazin-5-ium-3-olate **85** (86JHC375). Pharmaceutical compositions contain **83** (82FRP2486942).



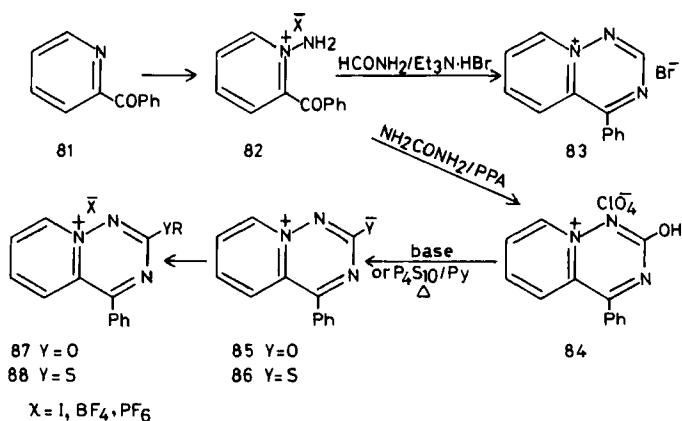
SCHEME 20



SCHEME 21

Methylation of **85** and the 3-thiolate **86** with MeI or $\text{Me}_3\text{O}^+\text{PF}_6^-$ gave only the 3-OMe **87** ($\text{R} = \text{Me}$) and 3-SMe **88** ($\text{R} = \text{Me}$), respectively. Similarly, phenylation of **85** or **86** with $\text{Ph}_2\text{I}^+\text{BF}_4^-$ gave **87** ($\text{R} = \text{Ph}$) or **88** ($\text{R} = \text{Ph}$), respectively. The regioselectivity in methylation and phenylation of the 1- and 3-olates and thiolates has been studied. Mechanistic suggestions were given to rationalize the observed phenomena.

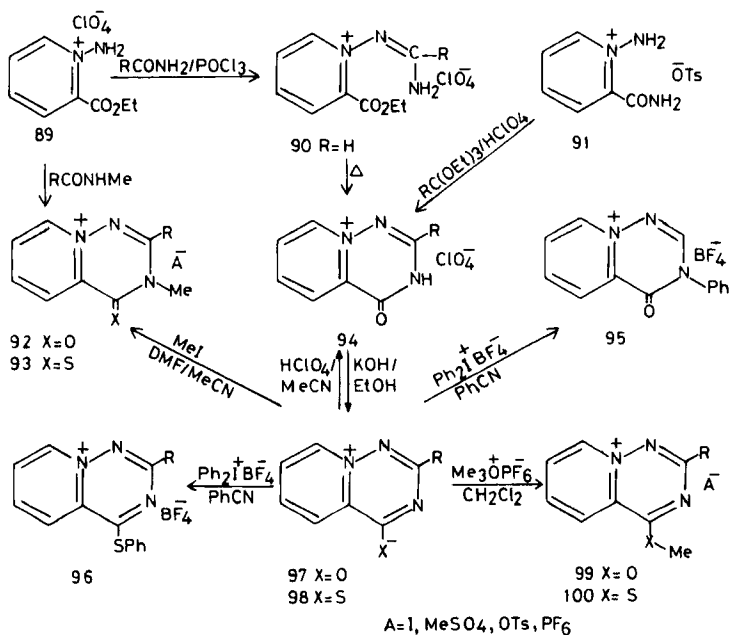
Further variation in the above synthesis utilizes picolinic acid ethyl ester *N*-aminium salts **89**. Compound **89** reacted with formamide in the presence of phosphorus oxychloride at room temperature to give **90**, which cyclized to **94** ($\text{R} = \text{H}$) on heating. Alternatively heating **89** with formamide gave **94**. This suggests that the reaction proceeds through the condensation of the amino group with the carbonyl moiety of formamide. This ring closure could be extended to other acid amides and *N*-methyl acid amides. The triazinium salts **94** reacted with base to give the stable zwitterionic pyrido[2,1-*f*][1,2,4]triazin-5-ium-1-olates **97** (86JHC375). The methylation of **97** has been studied (86JHC375). Photolysis of **90** gave picolinic acid amide (91H649).



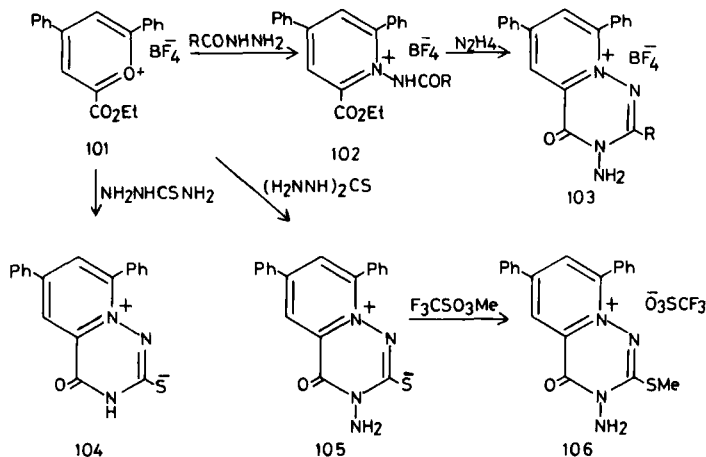
SCHEME 22

The reaction of 1-amino-2-carbamoylpyridinium tosylate **91** with *ortho* esters in the presence of perchloric acid gave **94** (88JHC437), which were converted to the zwitter ions **97** by the action of a base. Alternatively, **97** could be obtained by the reaction of **89** with alkyl and aryl cyanides. Reaction of **97** with perchloric acid gave **94**, whereas its reaction with phosphorus pentasulfide gave pyrido[2,1-*f*][1,2,4]triazinium-1-thiolates **98**. Methylation of **97** with methyl iodide gave **92**, whereas methylation with trimethyloxonium hexafluorophosphate gave a mixture of the hexafluorophosphates **92** and **99**. These results were significantly different in the case of the 1-thiolates **98**, where methylation with methyl iodide gave **100**, whereas by using trimethyloxonium hexafluorophosphate a mixture of *N*-methyl **93** and *S*-methyl **100** derivatives was formed. Phenylation of **97** and **98** with diphenyliodonium tetrafluoroborate gave **95** and **96**, respectively.

Reaction of 2-(ethoxycarbonyl)-4,6-diphenylpyrylium tetrafluoroborate **101** with aroylhydrazines gave pyridinium salts **102**, which cyclized with hydrazine to give pyrido[2,1-*f*][1,2,4]triazin-9-ium salts **103** (86S234). Cyclization of **101** with 3-thiocarbazide gave the dihydropyridotriazine **105** whose methylation gave **106** (84S697). On the other hand, reaction of **101** with thiosemicarbazide gave **104** (87H2183).



SCHEME 23

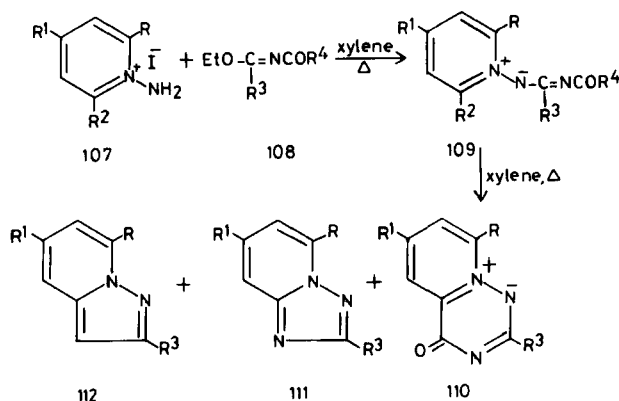


SCHEME 24

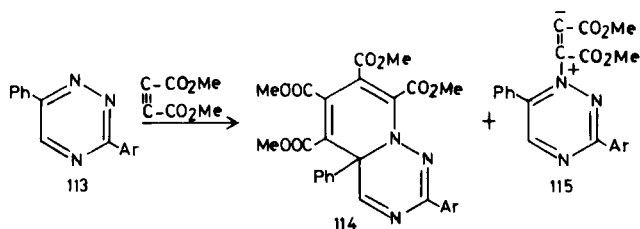
Thermolysis of 1-imidoyliminopyridinium *N*-ylides **109** gave the pyridotriazines **110** in addition to **111** and **112** (76CL413; 77JOC443). Compounds **109** were obtained by the reaction of pyridinium salts **107** with **108**.

Triazines **113** reacted with dimethyl acetylenedicarboxylate in acetic acid-acetic anhydride to give pyridotriazines **114** and minor quantities of the inner salts **115**, which were too unstable to purify (77LA1421).

Cycloaddition of triazine derivatives **116** ($\text{R}^2 = \text{H}$) with spiroheptatriene **117** gave cyclopenta[*c*]pyrido[2,1-*f*][1,2,4]triazines **118** (75LA1445). On the other hand, reaction of **116** ($\text{R} = \text{R}^2 = \text{H}$, $\text{R}^1 = \text{Ph}$) with **117** gave the isomeric structure **119**.



SCHEME 25



SCHEME 26

B. [1,2,4]TRIAZINO[*x,y-z*]QUINOLINES

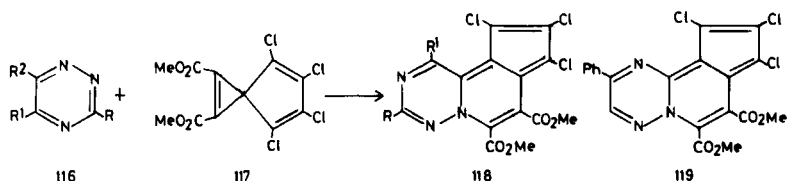
Eight isomeric structures can be drawn for the 1,2,4-triazino-quinolines, which have fusion only on the heterocyclic ring. Fusion could also exist on the benzo ring. Only six isomers were reported during the period of this review.

1. [1,2,4]Triazino[4,3-*a*]quinolines

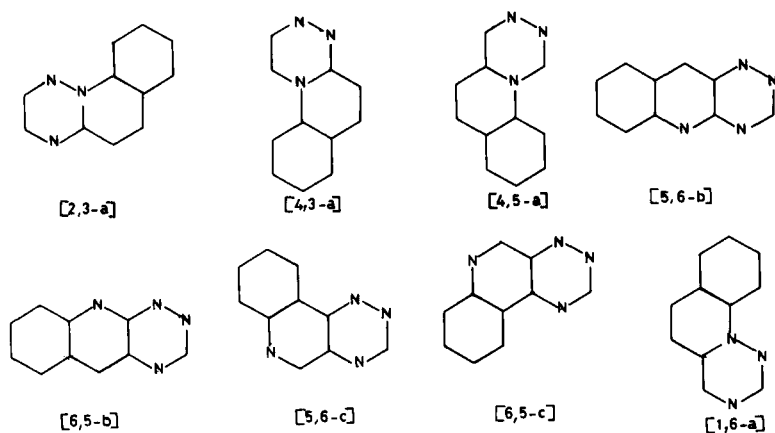
The triazinoquinolines **120** were obtained (80CZ203) by treating the phenacylquinolinium bromides with hydrazine. Cyclization of 2-hydrazinocinchonic acid with pyruvic acid gave **121** (91KGS1227).

2. [1,2,4]Triazino[5,6-*b*]quinolines

3-Oxo-2,3,4,10-tetrahydro[1,2,4]triazino[5,6-*b*]quinoline and some of its derivatives represented the first examples of this ring system (82JHC313). Thus, 2-nitrobenzyltriazines **124**, prepared by the cyclization of the *Z*-form of 2-nitrophenylpyruvic acid semicarbazone **122**, were reduced to amine derivatives **126a** by catalytic reduction (82JHC309). The desired structures **127** were then obtained by forming the pyridine ring through dehydration of **126** under catalysis of acetic acid. Thermal cyclization of **126a** was not satisfactory since the products were not pure enough. Two



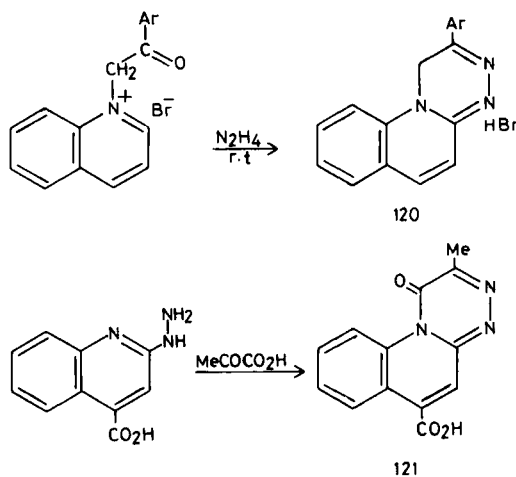
SCHEME 27



SCHEME 28

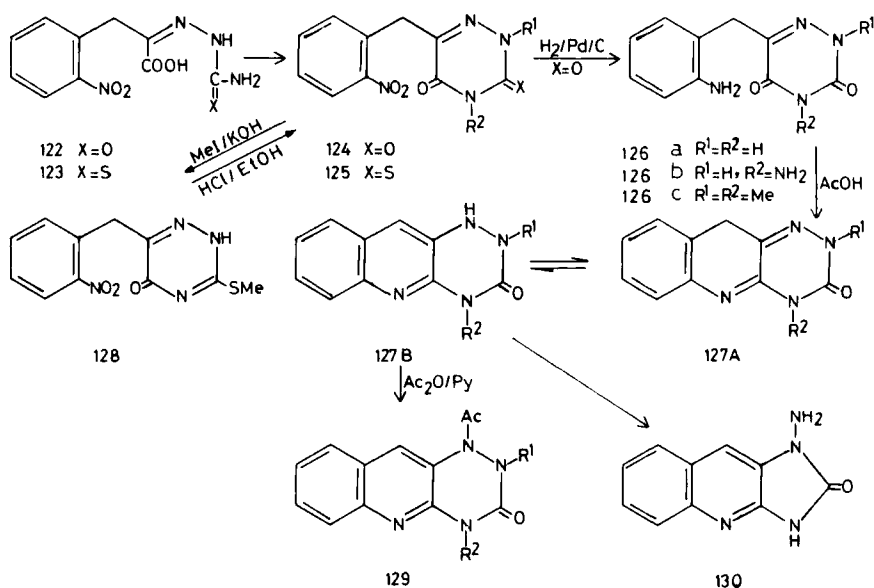
tautomeric forms of compounds **127** were possible where IR spectroscopy supported form **127A**, whereas PMR spectroscopy supported form **127B**. Acetylation of **127** was found to take place on **127B** to give **129**.

A more convenient method for the preparation of this ring system started with thiosemicarbazone **123**, whose alkaline cyclization to 2-thio-5-(o-nitrobenzyl)-6-azauracil **125** proceeds smoothly (84CCC2628). In contrast to the above method, it is not necessary to isolate the Z-form of thiosemi-



SCHEME 29

carbazone as done for semicarbazone. The thio derivative **125** was transformed to the 6-azauracil **124** by both oxidation with permanganate or methylation to give **128** and subsequent acid hydrolysis. The selective reduction of nitroderivative **124** was achieved by application of iron(II) sulfate in a weakly alkaline medium to give 5-(*o*-aminobenzyl)-6-azauracil, whose cyclization to **127** ($R^1 = R^2 = H$) was achieved by boiling in ethanol in the presence of acetic acid. Compound **127** ($R^1 = R^2 = H$) is transformed in acid medium to 1-amino-1,2-dihydroimidazo[4,5-*b*]quinolin-2-one **130**.

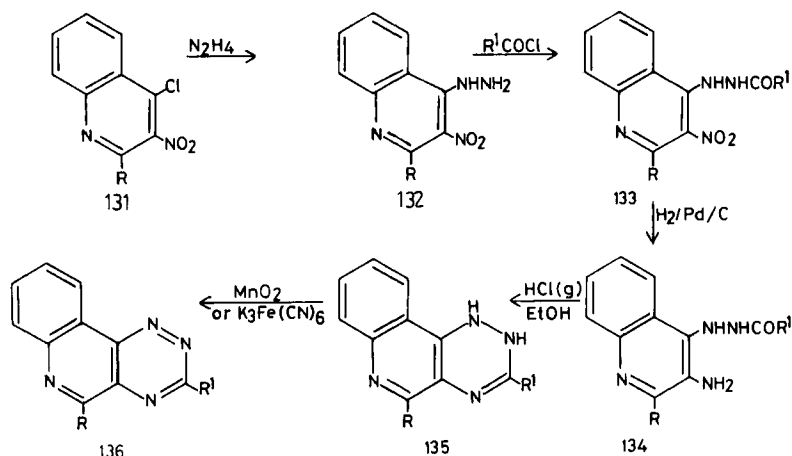


SCHEME 30

3. [1,2,4]Triazino[5,6-*c*]quinolines

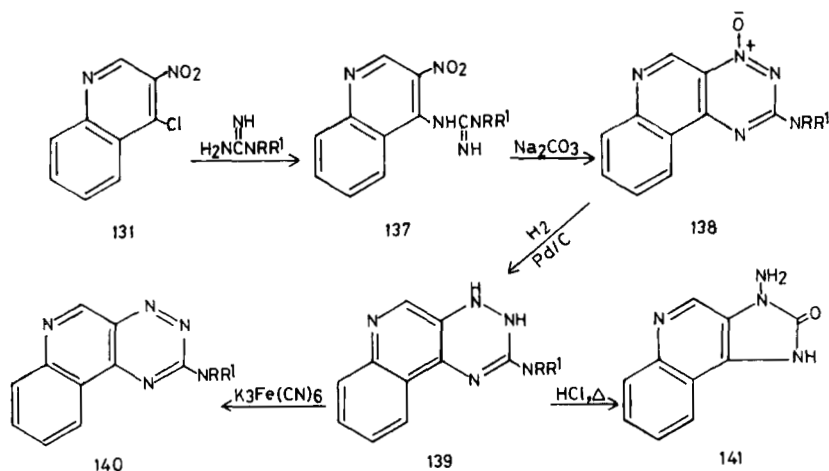
The synthesis of this ring system is based on the starting material 4-chloro-3-nitroquinoline and its derivatives **131**, whose reaction with hydrazine gave **132**. Its acylation gave **133**, alternatively prepared by reaction of **131** with acyl hydrazines. Catalytic hydrogenation of **133** gave the amino derivative **134**, which cyclocondensed to **135**. Subsequent dehydrogenation gave the [1,2,4]triazino[5,6-*c*]quinoline **136** (76M15; 84M12; 89JMC2474). Alternatively, the dihydro derivatives **135** were obtained from **132** by treatment with *ortho* esters in the presence of *p*-toluene-sulfonic acid (PTSA) and hydrogenation (75BRP1382781). Their anti-inflammatory activity was assessed in rats (75BRP1382781). Correlations

among biological activity and polarographic, spectral, and structural parameters in a series of 1,2,4-triazine derivatives were studied (81EUP38528; 84MI1).



4. [1,2,4]Triazino[6,5-*c*]quinolines

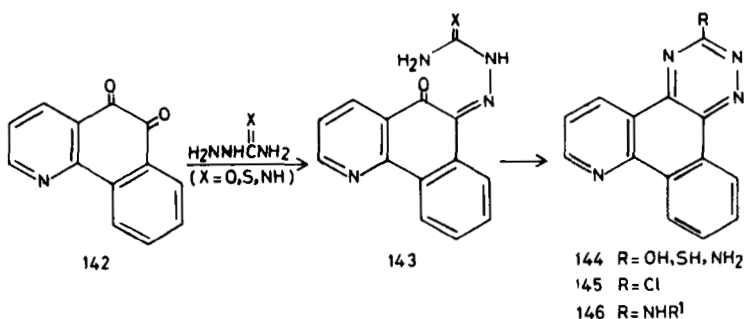
Reaction of 4-chloro-3-nitroquinoline **131** with guanidine or its derivatives gave 4-guanidine-3-nitroquinolines **137**, which lost water in alkaline medium and cyclized to [1,2,4]triazino[6,5-*c*]quinoline *N*-oxides **138** (74MI4; 76ACH395, 76MI4). Catalytic hydrogenation of the *N*-oxide gave the 1,2-dihydro compounds **139**, which could be isolated only as salts (81JHC1537). Without salt formation, the base underwent aromatization by oxidation with potassium ferricyanide to give **140**. Compound **139** transformed by heating to the *N*-aminoimidazoquinoline **141**. The mechanism of this transformation was studied using (81JHC1537) partial ¹⁵N-labeling. Compounds **138** have antibacterial, antifungal, and anti-inflammatory activities (74MI4). Electron impact fragmentations of 2-amino[1,2,4]triazino[6,5-*c*]quinolines and their derivatives have been investigated (85OMS416). The main primary decomposition route of both the singly and the doubly charged molecular ions is N₂ loss. Further fragmentation consists of radical eliminations from the 2-amino group with cleavage of the α- and β-bonds. A significant substituent effect is found, suggesting an intramolecular cyclization reaction with substituent migration.



SCHEME 32

5. [1,2,4]Triazino[5,6-f]quinolines

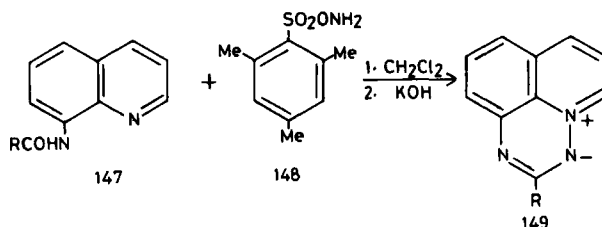
The benzo analogue has been prepared by condensation of benzo[*h*]quinoline-5,6-dione **142** with semicarbazide, thiosemicarbazide, and aminoguanidine, which occurred regioselectively at the 6-position and gave rise to the hydrazone derivatives **143**, which cyclized (83JHC1255) to the triazinobenzoquinolines **144**. Chlorination of **144** ($R = OH$) with phosphorus oxychloride gave **145**, which was converted to a variety of amino, hydrazino, and arylidene hydrazino derivatives **146** (83JHC1255).



SCHEME 33

6. Miscellaneous

Heterocycle **149**, having fusion at two edges of the quinoline ring and two edges of the triazine ring, was prepared (77H281) by the reaction of 8-acylaminoquinoline **147** with *o*-mesitylenesulfonylhydroxylamine **148**.



SCHEME 34

C. [1,2,4]TRIAZINO[*x,y-z*]ISOQUINOLINES

There are seven isomeric structures reported for this ring system during the period of this review.

1. [1,2,4]Triazino[3,2-*a*]isoquinolines

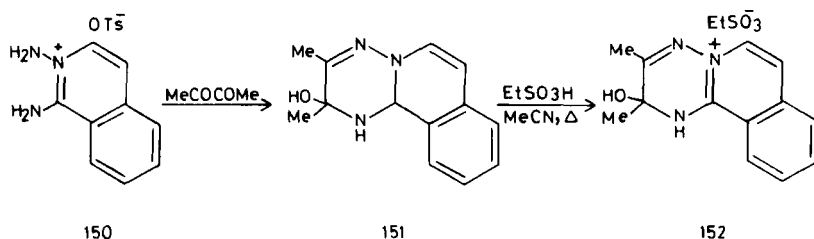
The triazinoisoquinoline **151** was prepared by cyclocondensation of the diaminoisoquinoline derivative **150** with biacetyl. Treatment of **151** with ethanesulfonic acid in acetonitrile gave the triazinoisoquinolinium salt **152**, which is useful as a local anesthetic, antidepressant, tranquilizer, sedative, and muscle relaxant (89GEP3833615).

2. [1,2,4]Triazino[3,4-*a*]isoquinolines

Cyclization of 1-hydrazinoisoquinoline **153** with diethyl oxalate gave a mixture of triazinoisoquinoline **154** and triazoloisoquinoline **155** (75CB3799). Oxidation of the pyrazolinyloisoquinolines **156** with potassium permanganate gave the hydrazone derivatives **157**, which cyclized (75CB3799) to the triazinoisoquinolines **158**. Oxidation of **158** gave **159**.

Condensation of 2-phenacyloisoquinolinium bromide **160** with hydrazine gave triazinoisoquinoline **161** (76KGS372).

The tetracyclic [1,2,4]triazino[4,3-*f*]phenanthridines **162** showed fungicidal activity, where they appeared to be the key requirements for control of *Erysiphe graminis tritici* (90MI3).



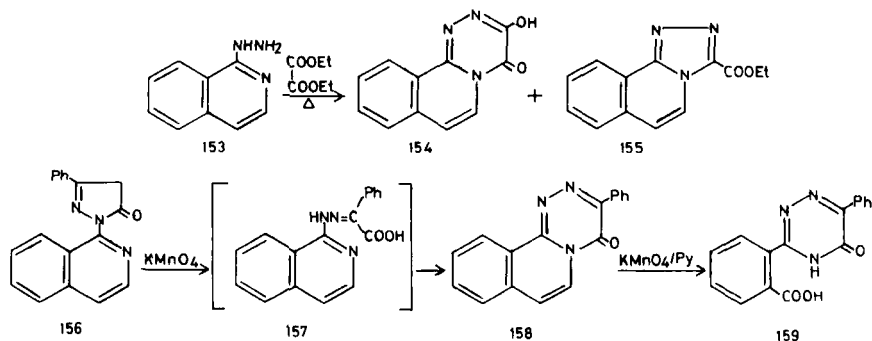
SCHEME 35

3. [1,2,4]Triazino[6,1-a]isoquinolines

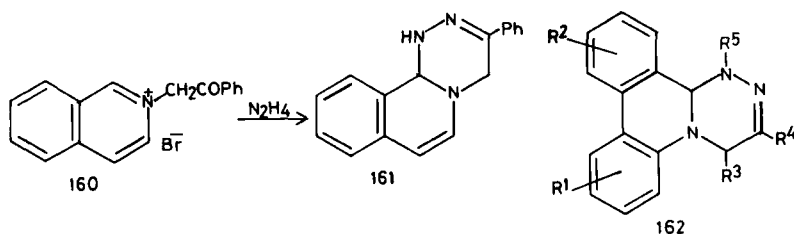
This ring system was prepared by treatment of the isoquinoline derivative **163** with *O*-tosylhydroxylamine followed by perchloric acid to give the aminoisoquinoline perchlorate **164**, which was cyclized by treatment with formamide to give the triazinoisoquinoline **165** (87GEP3715076). Treatment of the triazinoisoquinolinium salt **166** with sodium ethoxide gave the zwitterionic structure **167**. Analogues of **165** ($A = \text{C1}$) were prepared as central nervous system agents. The triazinoisoquinolinium sulfonate **165** ($A = \text{EtSO}_3$) showed considerable activity in pharmacological tests (89AF775). It exhibited a minimal sedative effect. Its metabolism *in vitro* and *in vivo* was studied using rat liver microsomes (87MI3). Various analogues of **167** showed antidepressant, antiarrhythmic, and antiparkinsonian activity (85BEP900598).

Heating the triazinoisoquinoline **168** with phosphorus oxychloride in presence of acetic acid and perchloric acid gave the triazinoisoquinolinium perchlorate **169** (85BEP900597), a useful antidepressant.

Photolysis of [1,2,4]triazino[6,1-a]isoquinolinium-1-olate **170** gave the acid amide **171** (91H649).



SCHEME 36



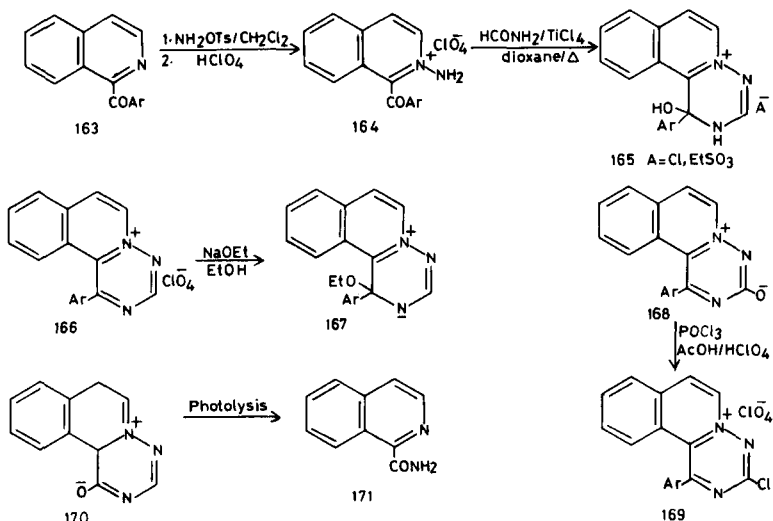
SCHEME 37

4. [1,2,4]Triazino[2,3-*b*]isoquinolines

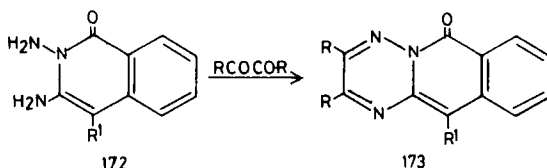
Cyclization of 2,3-diaminoisocarbostyrils **172** with α -diketones gave 6*H*[1,2,4]triazino[2,3-*b*]isoquinolin-6-ones **173** (75YZ340). The emission characteristics of **173** were studied (83YZ1283).

5. [1,2,4]Triazino[5,6-*c*]isoquinolines

The synthesis of 6-oxo-2,3,4,6-tetrahydro[1,2,4]triazino[5,6-*c*]isoquinoline-3-thione **178** was achieved by the reaction of the keto acid **174** with thiosemicarbazide to give azauracil **175**. Its esterification gave **176**, which was converted to the amide **177** and cyclized (84PHA186; 92CCC123) in presence of acetic acid to give **178**.



SCHEME 38



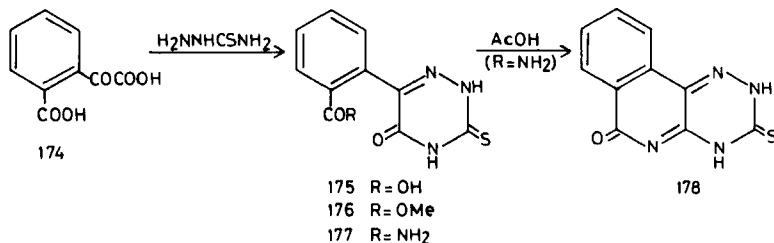
SCHEME 39

Alternatively, the starting material has the isoquinoline ring, as in phthalonimides **179**, which on reaction with thiosemicarbazide or aminoguanidine gave the intermediates **180**, which were subsequently cyclized (75ZOR2407) with base to give **181**.

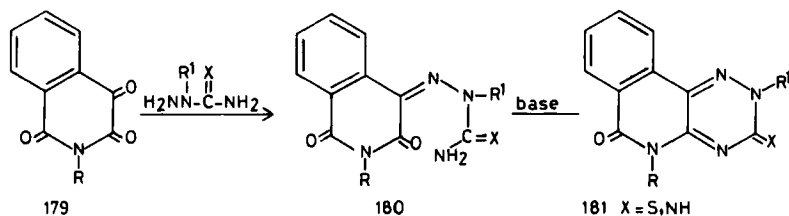
The related aza analogue of this ring system, triazino[6,5-*f*][1,7]naphthyridine **184** was prepared (86PHA284) by the cyclization of azaauracyl-picolinic acid **183** with ammonia in the presence of DCC. The starting material was prepared from 2-carboxy-3-pyridylglyoxylic acid thiosemicarbazone **182**.

6. [1,2,4]Triazino[6,5-*c*]isoquinolines

2-Thioxo-2,3-dihydro[1,2,4]triazino[6,5-*c*]isoquinolin-6-one **189** was obtained (75ZOR2407) by the cyclization of the 3-thiosemicarbazone **188** with alkali. Compound **188** was prepared by the reaction of 3-anilino-1,4-dihydro-1,4-isoquinolinedione **187** or the ether **186** with thiosemicarbazide. Compound **187** was obtained by reaction of the ether **186** in benzene with aniline. The ether **186** was obtained from the alkylation of **179** ($R = H$) via its silver salt **185**.



SCHEME 40



SCHEME 41

III. Pyrano[1,2,4]triazines

A. PYRANO[x,y-z][1,2,4]TRIAZINES

Although there are four possible isomeric ring systems for this combination, only three examples have appeared in recent literature.

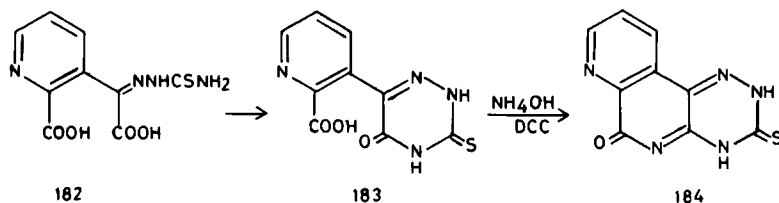
1. *Pyrano*[3,4-*e*][1,2,4]triazines

The benzo analogue **191** was prepared (86JHC721) by the condensation of 2,2,6-trimethylchromane-3,4-dione **190** with formamidine or its derivatives.

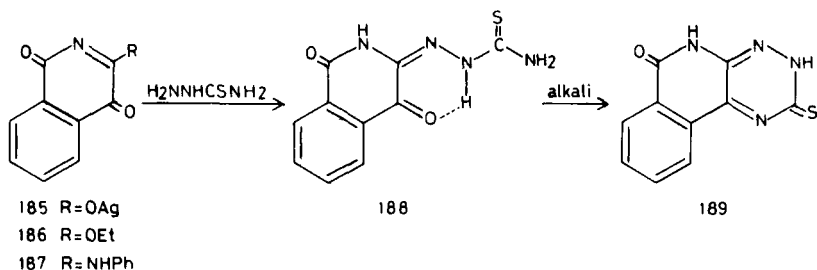
2. *Pyrano*[4,3-*e*][1,2,4]triazines

A series of 3-aryl-5,8-dihydro-6,6,8-trimethyl-5,8-ethano-6*H*-pyrano [4,3-*e*][1,2,4]triazine-4-oxides **193** was prepared (79JHC1389) by boiling a mixture of **192** and trimethyl *ortho*-arylates. The effect of substituents on the chemical shifts of their ^{13}C NMR spectra was studied.

A series of the benzo derivatives **194** was prepared (86JHC721) by treatment of the corresponding triazinone **194** (R = OH) with phosphorus oxychloride to give the chloro derivatives, whose reaction with nucleophiles gave the respective hydrazino, azido, and amino derivatives.



SCHEME 42



SCHEME 43

3. *Pyrano*[2,3-*e*][1,2,4]triazines

The benzo analogues otherwise named triazino[5,6-*c*]isocoumarines **195**, were prepared by the cyclization of **175** with DCC (92CCC123).

IV. Diazino[1,2,4]triazines

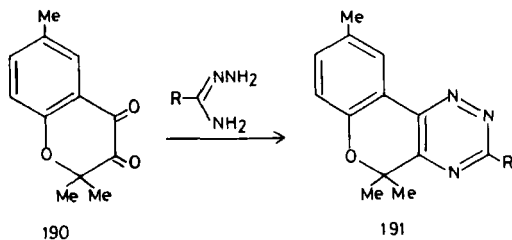
A. [1,2]DIAZINO[*x,y-z*][1,2,4]TRIAZINES

1. *Pyridazino*[2,3-*b*][1,2,4]triazines

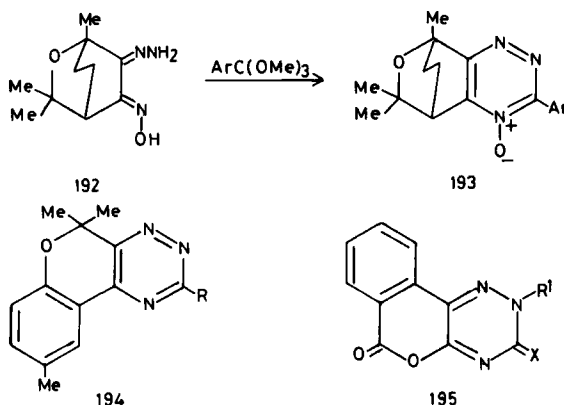
Pyridazino[2,3-*b*]benzo[1,2,4]triazine **197** was prepared (84CL1197) by boiling the triazolobenzotriazole **196** with dimethyl acetylenedicarboxylate in toluene. Compound **197** behaves as a stable free radical.

2. *Pyridazino*[6,1-*c*][1,2,4]triazines

Reaction of the oxazolo[3,2-*b*]pyridazinium perchlorates **198** with hydrazine hydrate and methylhydrazine furnish (82CPB1557) hemiperchlorates of pyridazinotriazines **199** and pyridazinotriazinium perchlorate **200**,



SCHEME 44



SCHEME 45

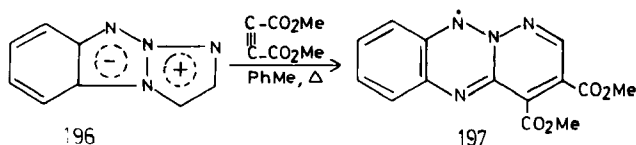
respectively. In the reaction of **198** with hydrazines, the initial attack of the reagent always occurs at the C-8a position.

Cyclization of ethyl 3-cyano-3-methyl butyrate **201** with hydrazine hydrate gave the hydrazonopyridazine **202**, which underwent ring closure with oxalyl chloride to give (85MIP1) pyridazinotriazine derivative **203**.

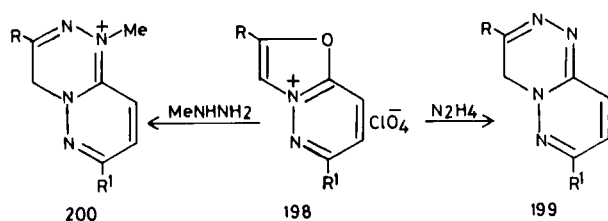
Cyclization of the hydrazonopyridazine derivative **204** with polyphosphoric acid gave [84JAP(K)59206363] the pyridazinotriazine **205**. Amination of the latter with **206** afforded **207**, which showed antihypertensive activity. The [1,2,4]triazino[4,3-*b*][1,2,4]triazolo[3,4-*f*]pyridazine derivatives **209** were prepared either by ring closure of **208** in polyphosphoric acid or by the action of triethyl *ortho*-formate on **211** (86M867, 86MI5). Similarly, the triazino[4,3-*b*][1,2,4]triazolo[3,4-*f*]pyridazine **210** was prepared from **212** (86MI5). The structure of **209** indicated that a further reaction, owing to pyruvate exchange with the starting material **208**, had taken place. Compound **209** showed a positive inotropic effect.

3. Pyridazino[4,5-*e*][1,2,4]triazines

The pyridazinotriazines **214**, prepared from **213**, showed [84JAP(K)59116201; 87MI1] a broad herbicidal spectrum against several



SCHEME 46



SCHEME 47

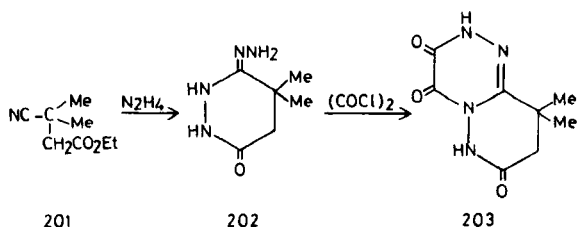
weeds and selective activities to such crops as rice, corn, wheat, and soybean. Their activities as photosynthesis inhibitors were also evaluated by an oxygen electrode method (87MI1).

4. [1,2,4]Triazino[5,6-c]cinnolines

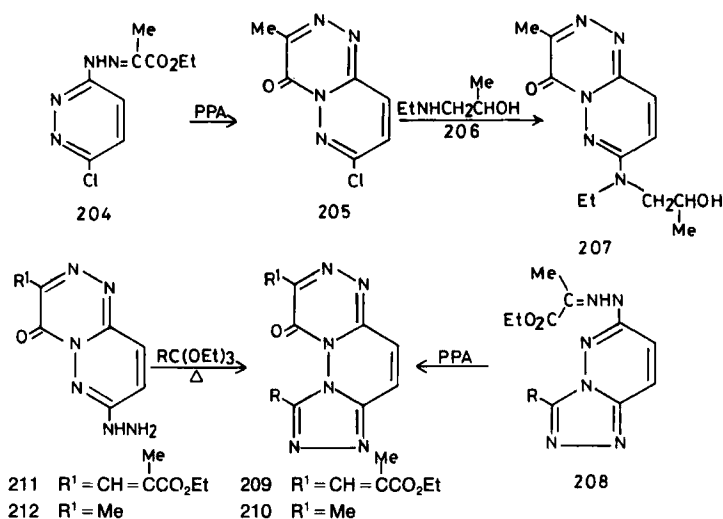
Azo coupling of the diazonium salt **215** ($X=O$) with cyanoacetylcarbamate or diethylmalonyl biscarbamate **216** in aqueous sodium acetate gave the hydrazone **217** ($X=O$), which was cyclized by acid under hydrolytic splitting of the carbonyl component to give 2,3,4,6-tetrahydro[1,2,4]triazino[5,6-c]cinnoline-3-ones **218** ($X=O$) (79CCC2438). It was also obtained by reduction of the diazonium salt with alkaline sulfite and subsequent cyclization of the formed hydrazine salt in acidic medium. The same procedure was used for the synthesis of the thio analogue as shown in the Scheme 51 (86MI1).

5. [1,2,4]Triazino[3,4-a]phthalazines

Hydralazine **219** is a good precursor for that ring system. Its reactions with pyruvic acid (75JOC2901), arylidene pyruvic acids (81AP1030), and 4-aryl-2-oxo-butanoic acids (87JHC63) gave the respective hydrazones **220**, which were cyclized by acetic acid or polyphosphoric acid to give **221**. The esters cyclized directly. Thus, when the reaction of **219** with



SCHEME 48

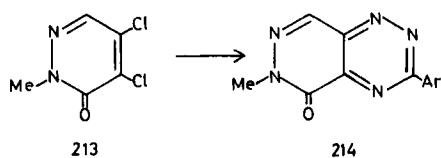


SCHEME 49

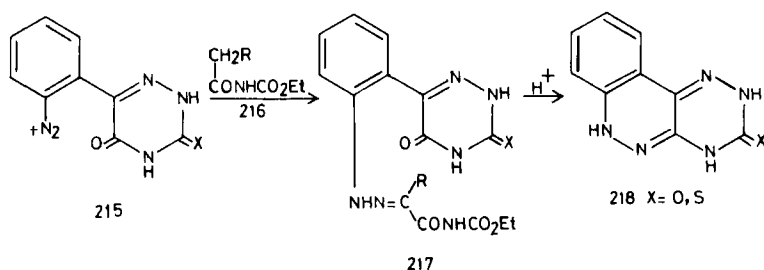
ethyl aroylpyruvate (83JHC1231; 87H1853) was carried out under acidic conditions, it gave directly **222** in addition to the formation of a product resulting from a simultaneous elimination of the appropriate acetophenone. The reactions of the 4-substituted hydralazines with ketoacids afforded similar products and the reaction with diethyl oxalate gave 3,4-dioxo[1,2,4]triazino[3,4-*a*]phthalazines (75JOC2901; 91PHA105).

Cyclocondensation of 2-arylbenzoic acid **223** with hydrazine gave the phthalazine derivative **224**, which was alkylated with ethyl chloroacetate in aqueous sodium hydroxide or pyridine to give the N-substituted derivative **225**. Condensation of the latter with hydrazine afforded the hydrazide **226**, which could be cyclized to give the 2*H*[1,2,4]triazino[3,4-*a*]phthalazin-3(4*H*)-one **227** (91MI3).

Treatment of 1-chlorophthalazine **228** with alkoxide or sec-amines gave **229**, whose reaction with phenacyl halides afforded **230**. Cyclocondensation of the latter with hydrazine gave **231**. Aromatization of **231** with tetrachlorobenzoquinone (TCBQ) gave (89FES29) the triazinophthalazine



SCHEME 50



SCHEME 51

232. Alternatively, **232** was obtained by cyclocondensation of **233** with phenacyl halides in the presence of acetic acid and subsequent reaction of the formed triazinophthalazine with alkoxides or sec-amines (89FES29).

Compounds **227** and **232** were tested *in vitro* for inhibition of [³H]-diazepam-specific binding to benzodiazepine receptors in membranes from synaptosomes of rat brain and *in vivo* for their effects on conditioned behavior in rats (89FES29).

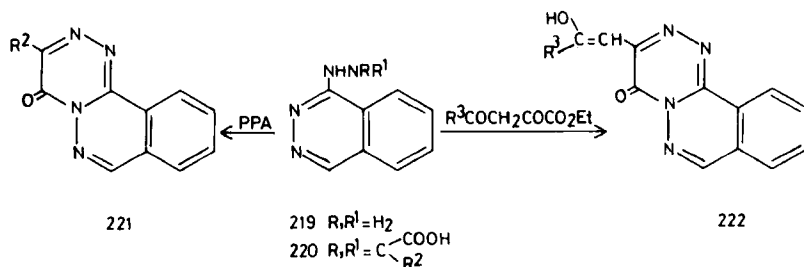
B. [1,3]DIAZINO[x,y-z][1,2,4]TRIAZINES; PYRIMIDO[x,y-z][1,2,4]TRIAZINES

The relevant heterocycles that belong to this type of ring system are the pyrimido[x,y-z][1,2,4]triazines and the [1,2,4]triazino[x,y-z]quinazolines.

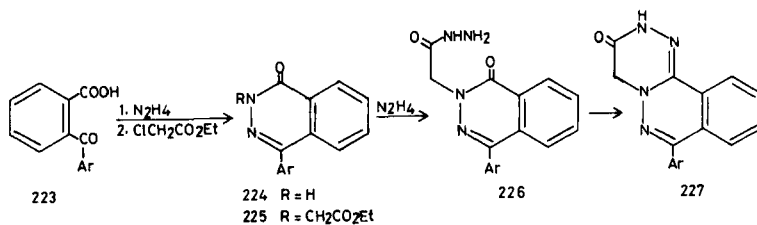
There are 10 possible isomeric structures, two on each side of the triazine ring except side a, as shown in Scheme 55.

1. Pyrimido[1,2-b][1,2,4]triazines

The reaction of 3-amino-2-hydrazino-4(3H)-pyrimidinones **234** with dimethyl acetylenedicarboxylate gave pyrimidinylidene hydrazones **236**



SCHEME 52



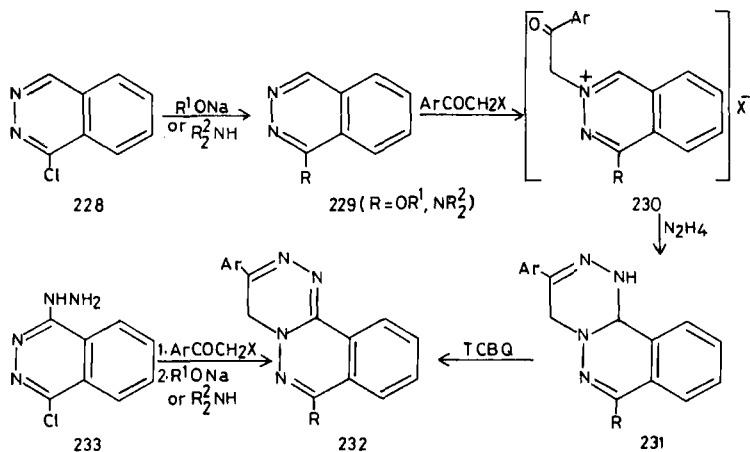
SCHEME 53

formed by tautomerism from the initial adducts **235**. The hydrazones **236** underwent (88JHC739) a thermal rearrangement to pyrimidotriazines **239** via an initial ring opening of **236** to give **237** followed by two cyclocondensation sequences to give **238** and then **239**.

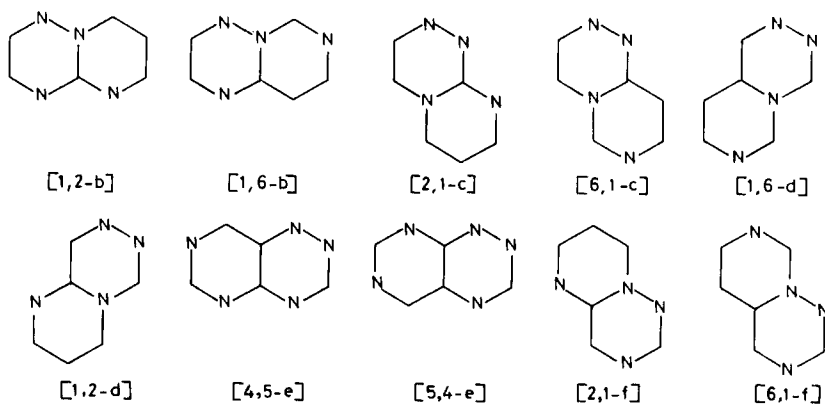
2,3-Diamino-4(3*H*)pyrimidinones on reaction with α -diketones give (84JHC1537; 85JHC1317) pyrimido[1,2-*b*][1,2,4]triazines **240**. Similarly, the condensation of 2,3-diamino-4(3*H*)pyrimidinones with cyclohexandione, 1,2-naphthoquinone, acenaphthenequinone, and phenanthraquinone gives the respective condensed pyrimidotriazines of general structure **241** (85JHC1317).

2. Pyrimido[1,6-*b*][1,2,4]triazines

The synthesis of diphenylmethylpyrimidotriazinones **243** was achieved (86MI2) by the reaction of 3-chloro-5,6-diphenyl[1,2,4]triazine with chloro- or cyanoacetamides in pyridine to give **242**, which cyclized with sodium acetate in acetic acid.



SCHEME 54



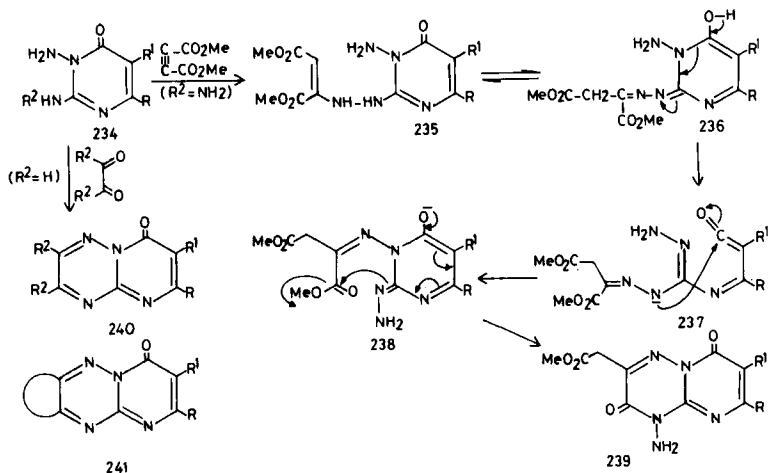
SCHEME 55

Some derivatives of pyrimido[1,6-*b*][1,2,4]triazines **245** have been prepared (88SC805) as potential anticancer agents by reaction of the triamino-pyrimidinethione **244** with pyruvic acid, followed by alkylation.

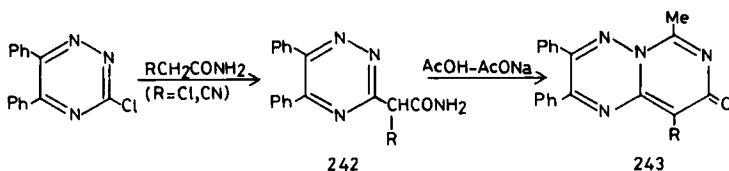
3. Pyrimido[2,1-*c*][1,2,4]triazines

Cyclocondensation of 2-hydrazinopyrimidine derivative with dimethyl acetylenedicarboxylate gave pyrimidotriazinones **246** (84GEP3302413).

Examples of this ring system were found in several tricyclic systems. Treatment of the pyrazolo[3,4-*d*]pyrimidines **247** with sodium borohydride



SCHEME 56



SCHEME 57

gave 4,5-dihydro-1*H*-6-chloropyrazolopyrimidine **248**, whose alkylation with ethyl bromoacetate afforded *N*-alkyl derivatives **249**. Reaction of the latter with hydrazine hydrate gave **250** (90JHC823), which are useful as potential blood platelet aggregation inhibitors.

The [1,2,4]triazolo[4',3':3,4]pyrimido[2,1-*c*][1,2,4]triazines **253** were prepared (75G1029) by cyclization of hydrazine **251** with phenacyl bromides, which took place via **252**.

Thermal cyclization of **254** afforded **255**, which reacted with hydrazine to give **256**. Heating a suspension of **256** in DMF gave 6,10-dihydro-6*H*-pyrido[3',2':5,6]pyrimido[2,1-*c*][1,2,4]triazin-5-one **259** via the intermediates **257** and **258** (86JHC509).

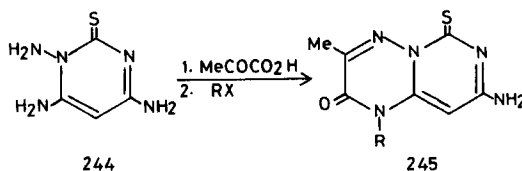
Pyrido[3,2-*e*]pyrimido[2,1-*c*][1,2,4]triazine derivatives were prepared, and the diuretic, natriuretic, and kaliuretic activities determined (90AF1349).

4. *Pyrimido*[6,1-*c*][1,2,4]triazines

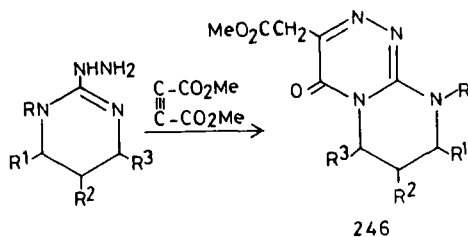
Cyclizations of 6-(1-alkylhydrazino)isocytosine **260** with the appropriate α -haloketones or ethyl bromopyruvate under acidic conditions gave (80JOC3919) exclusively the 6-amino-1,4-dihydro-8*H*-pyrimido[6,1-*c*]-[1,2,4]triazin-8-ones **261**.

Treatment of 3-methyl-6-(1-methylhydrazino)uracil **262** with phenacyl bromides in ethanol afforded (78H1571; 81CPB379) the pyrimido-[4,3-*c*][1,2,4]triazines **264** in addition to **263**.

This ring system is also present in the tricyclic heterocycles isoxazolo-[5',4':4,5]pyrimido[6,1-*c*][1,2,4]triazines. They were prepared (88JIC500)



SCHEME 58



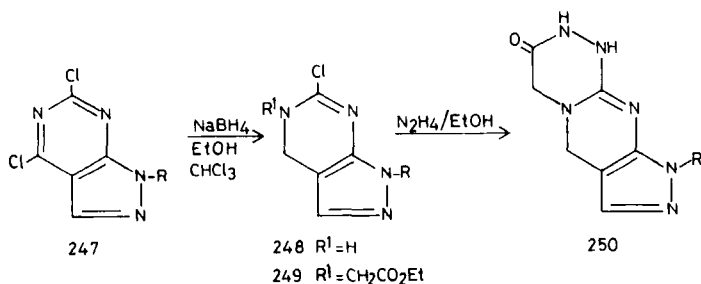
SCHEME 59

by the condensation of hydrazinoisoxazolopyrimidines **265** with chloroacetone and the products were cyclized to give isoxazolopyrimidotriazine derivative **266**, which exhibited bacterial and fungicidal activity.

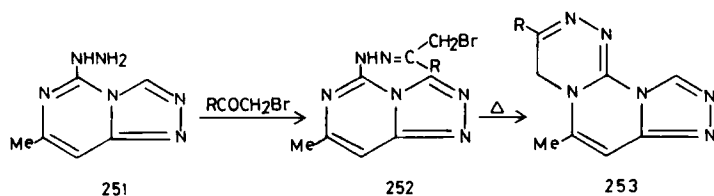
5. *Pyrimido[4,5-*e*][1,2,4]triazines*

The fusion of a pyrimidine ring on face *e* of the triazine leads to two isomeric ring systems where the site of fusion is [4,5-*e*] or [5,4-*e*]. The latter ring system includes some antibiotics, as will be shown later. Consequently, the former ring system stimulated interest in the analogues of the antibiotics. A review article that included these two ring systems appeared recently [92HC(24)261].

Ring system [4,5-*e*] may be prepared by the annulation of a triazine ring onto a preformed pyrimidine ring or vice versa. Thus, the synthesis of 1,3-dimethyl-6-azalumazines (isofervenuclins) **268** was carried out (78CPB367) by the cyclocondensation of the 6-amino-1,3-dimethyl-5-nitrosouracil **267** with acyl-, aroyl-, or heteroylhydrazines to give **268** and **269**. The latter was also obtained by treatment of **268** with 6-amino-1,3-dimethyluracil. Treatment of **268** with sodium sulfate in hot formic acid gave theophylline derivatives. Reaction of **267** with amino or alkylamino



SCHEME 60

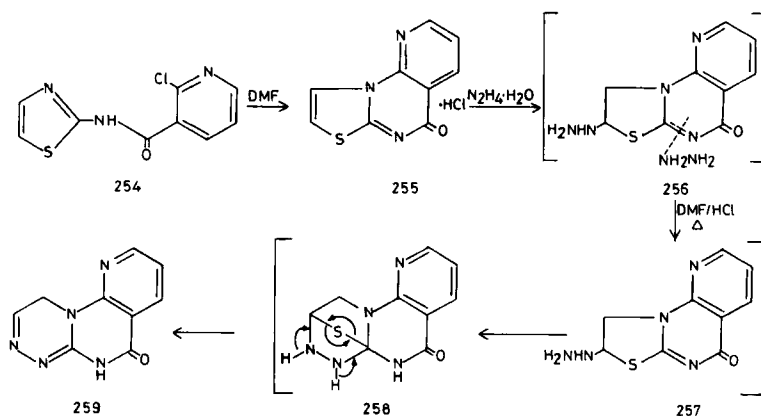


SCHEME 61

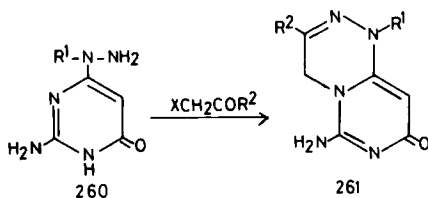
guanidines **270** gave **271** (75BCJ725). Oxidation of 7-aminotheophylline **273** gave the pyrimidotriazine **268** (81MI2; 83KGS1564). Condensation of dibromopyrimidines **272** ($\text{R} = \text{H}, \text{Me}$) with aminoguanidine derivatives **270** gave (75BCJ1679) the pyrimidotriazines **271**. Also, condensation of the dibromopyrimidine derivative **274** with aminoguanidine derivatives gave **275** (75BCJ1679).

Photochemical cyclization of 5-arylo-6-(dimethylaminomethyleneamino)-1,3-dimethyluracils under aerobic conditions gave 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7-ones **277** (77CPB2794). Reaction of 6-amino-5-(arylo)-1,3-dimethyluracils (**276**, $\text{R} = \text{H}$) with excess urea or *N,N*-carbonyldiimidazole gave the trioxypyrimidotriazine **277**, which underwent alkaline hydrolysis and then decarboxylation to give the triazine-diones **278** (78H1387; 80JHC1365). Fusion of the respective Schiff base of **276** ($\text{R} = \text{H}$) gave the pyrimidotriazine **279** (74JA5607) in addition to an imidazopyrimidine derivative.

An alternative synthesis of this ring system involved the construction of the triazine ring at the first stage. Thus, the reaction of diethyl oxomalonate either with thiosemicarbazide followed by methylation or with *S*-



SCHEME 62



SCHEME 63

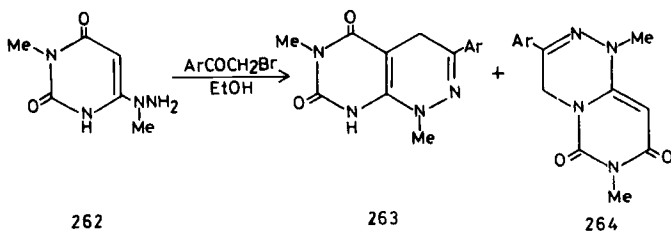
methylisothiosemicarbazide hydroiodide in acetic acid gave the [1,2,4]-triazine derivative **280**. Treatment of **280** with thionyl chloride yielded **281**, whose reaction with benzamidine or guanidine gave **282** (85JOC2293). On the other hand, reaction of the carbamoyl analogue **283** with phosphorus oxychloride gave **284**, whose cyclization was affected with benzamidine to give a 6-azapteridine **285** (85JOC2293).

Condensation of arylhyrazonooxomalononitrile with methyl isocyanate gave **286**, which could be cyclized to iminotriazinecarbonitrile **287** ($R = H$). Its reaction with phenyl isocyanate gave **287** ($R = \text{CONHPh}$), which was cyclized by the action of triethylamine to give **288** ($X = \text{NH}$), which was in turn hydrolyzed to **288** ($X = \text{O}$) (78HCA1175).

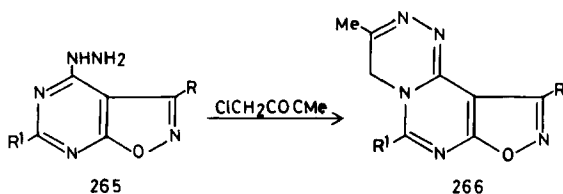
Thermolysis of 5-amino-6-azido-1,3-dimethylxanthine **289** in chlorobenzene gave 3-aminoisofervenuin **290** possibly through a C-nitrene intermediate (92MI1).

Derivatives of the pyrimido[4,5-*e*][1,2,4]triazines at the 7-position were prepared (75JOC2329) by displacement of the respective chloro derivatives. Reaction of pyrimidotriazines **291** or **294** ($R = \text{SO}_2\text{Me}$) with acetylenic alcohols or amines gave azalumazines **292** or azapterins **295**, respectively, with dienophilic side chains (88JOC800). Compounds **292** or **295** underwent intramolecular Diels–Alder reaction to give 6,7-annulated 5-deazapteridines **293** and **296**, respectively (88JOC3568).

7-(2'-Cyanophenoxy)-1,3-dimethyl-6-azalumazine **297** ($R = \text{CN}$), ob-



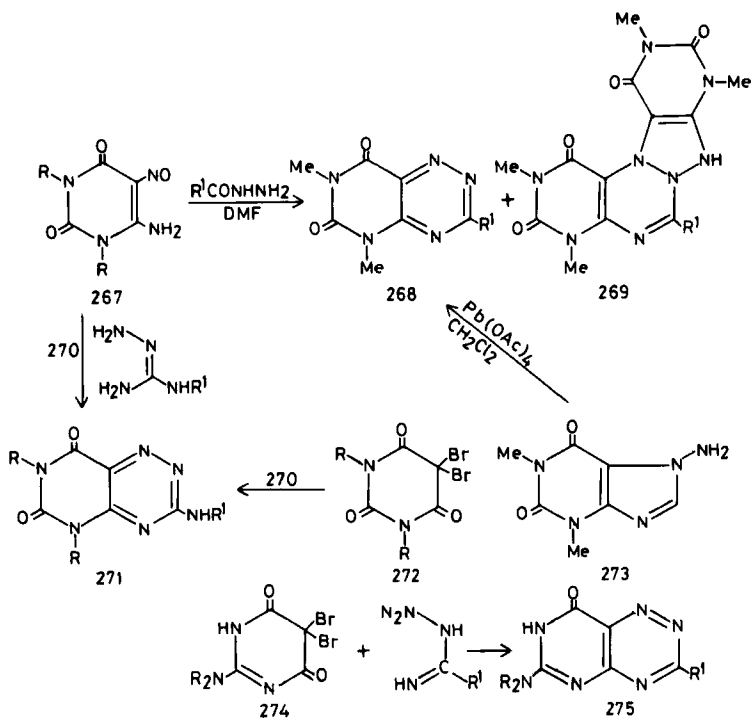
SCHEME 64



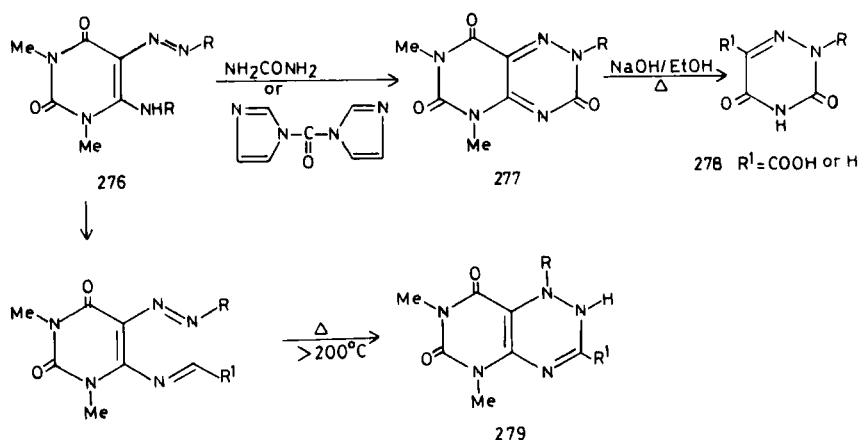
SCHEME 65

tained by the reaction of 7-chloro-1,3-dimethyl-6-azalumazine **268** with *o*-cyanophenol, underwent thermal intramolecular Diels–Alder reaction to give benzofuro[3',2' : 5,6] pyrazino[2,3-*d*]pyrimidin-2,4-dione **298** (87T5159). On the other hand, reaction of **268** R = Cl with salicylaldehyde *O*-methyloxime gave **297** (R = CH=NOMe), which did not give **298**.

Reaction of isoferrenulin **268** (R = H) with ketones in the presence of diethylamine or excess of the latter gave pyrido[2,3-*d*]pyrimidinedione **299** (R¹ = R² = H) and uracil derivative **300** (89KGS274; 90KGS1545).



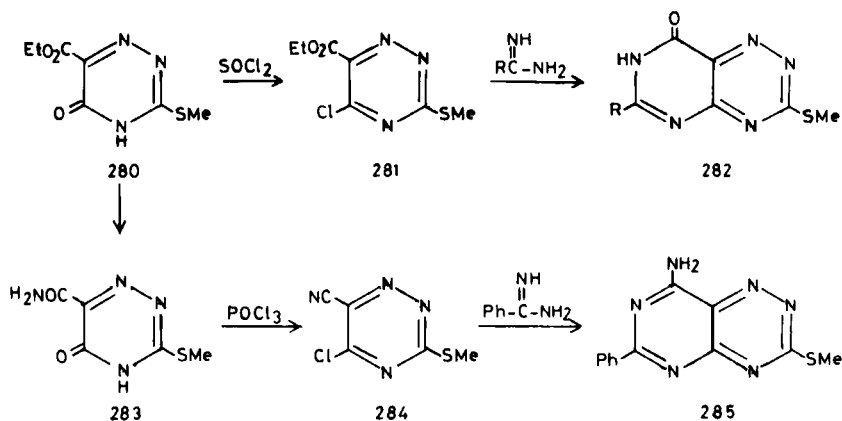
SCHEME 66



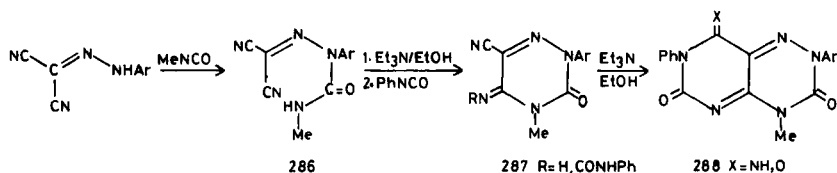
SCHEME 67

Treatment of isofervenuin with ketones in presence of $\text{BF}_3/\text{Et}_2\text{O}$ gave 5,6-disubstituted pyridopyrimidinediones **299** (87KGS1697) via a [4 + 2] cycloaddition reaction.

Hydrolysis of isofervenuins **268** with aqueous base occurred at the $\text{C}_2\text{—N}_3$ bond to give *N*-carboxy-*N*-methylcarbamoyltriazines **301**, which were transformed to **268** by acidification of the reaction mixture. On the other hand, base-catalyzed hydrolysis of **268** gave imidazo[4,5-*e*][1,2,4]triazines **302** (87KGS1555). Hydrolysis of the pyrimidotriazine derivatives with alkali gave the triazines **303** and **304** (77JPR522; 87JPR290).



SCHEME 68



SCHEME 69

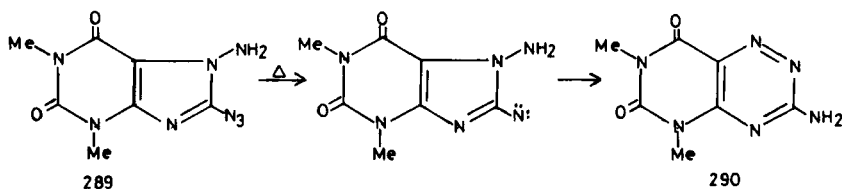
Cyclocondensation of (pivaloylamino)-(methylthio)azapterin **305** with 1-morpholinocyclopentene **306** gave 5,6-cyclopenteno-5-deazapterin **307** (87H2673).

The anti-inflammatory, analgesic, and antimicrobial activities of pyrimidotriazinedione derivatives have been investigated (80KFZ39).

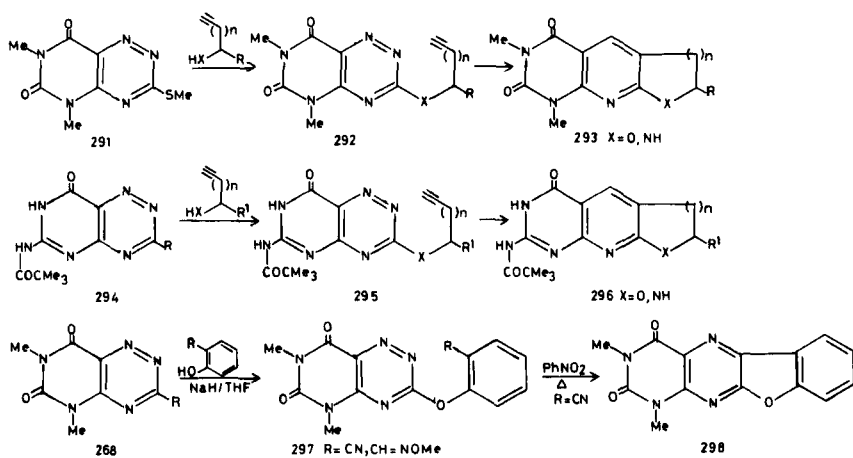
6. *Pyrimido[5,4-e][1,2,4]triazines*

The discovery of the potent but highly toxic antibiotics xanthothricin (toxoflavin) **308**, fervenulin **309**, and MSD-92 (2-methylfervenulone) **310** as naturally occurring derivatives of the pyrimido[5,4-*e*][1,2,4]triazine (7-azapteridine) stimulated interest in this ring system (73MI1). Moreover, reumycin **311** is not found in nature, but has useful pharmacological activity. Their synthesis as well as the synthesis of this ring system in general may be approached from a pyrimidine or a triazine followed by the formation of the bicyclic system. Most work has utilized the first approach.

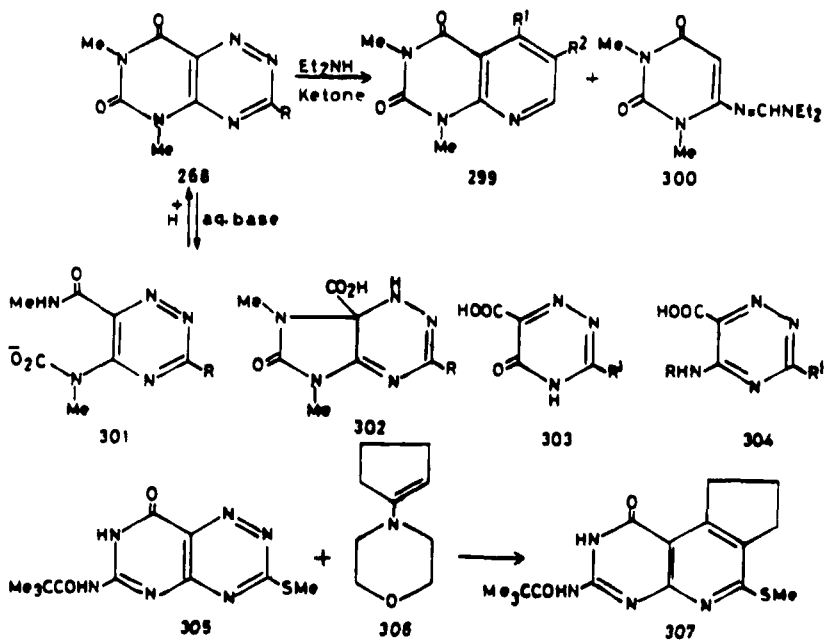
o-Aminohydrazinopyrimidines are useful precursors for the construction of this ring system. Thus, cyclization of the *o*-nitrohydrazino derivatives such as 3-methyl-6-(1-methylhydrazino)-5-nitrouracil (**312**), prepared by reaction of 6-chloro-3-methyl-5-nitrouracil with methylhydrazine, by reaction with aldehydes followed by catalytic hydrogenation gave a mixture of **313** and **314** (75S177). 3-Methyl-5-nitro-6-benzylidene hydrazinouracil was also cyclized to **314** (R = H). On the other hand, **314** (R = Me) was obtained by condensation of 6-amino-1,3-dimethyl-5-nitrouracil with hydrazones (76H1503).



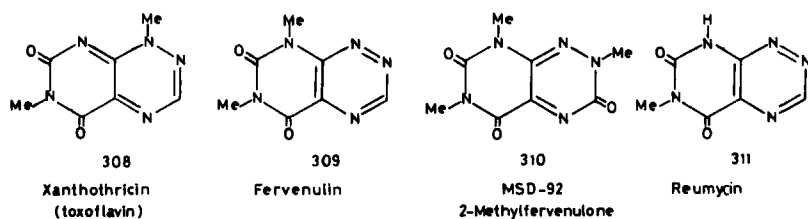
SCHEME 70



SCHEME 71



SCHEME 72

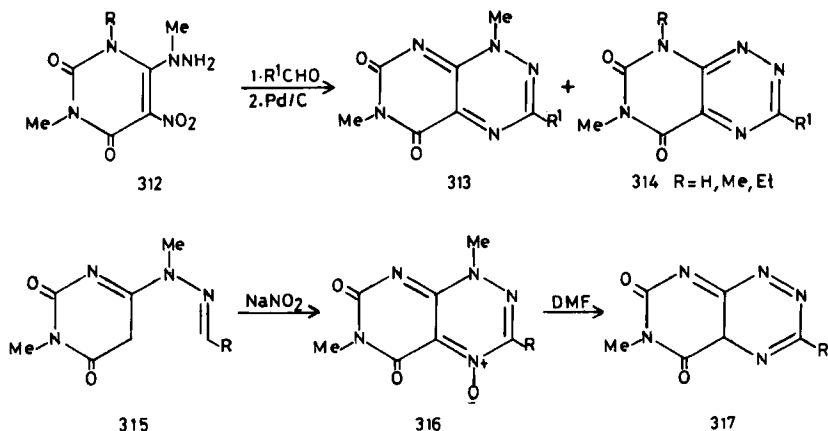


SCHEME 73

6-Benzylidenehydrazino-3-methyluracils were treated with sodium nitrite in acetic acid to give the corresponding 5-nitrosouracils. Dehydrative cyclization of the nitrosouracils with acetic anhydride gave 6-substituted 3-methyl-7-azalumazines **314** ($R = H$) (78CPB3154), whose ethylation gave 6-substituted-1-ethyl-3-methyl-7-azalumazines **314** ($R = Et$).

Toxoflavin and 4-oxides **316** were prepared by nitrosation and cyclization of hydrazones **315** (75CPB2001). The deoxygenation of the 4-oxides could be effected thermally [76JCS(P1)713]. Both toxoflavins and toxoflavin-4-oxides gave the corresponding 1-demethyltoxoflavins (8-demethylfervenuins) **317** by treatment with nucleophiles such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, or acetic acid (75CPB2001).

Both **316** ($R = Ph$) and the 4-oxide of **314** ($R = Me$) were similarly prepared from the respective hydrazones but in the presence of diethyl azodicarboxylate [76JCS(P1)713].



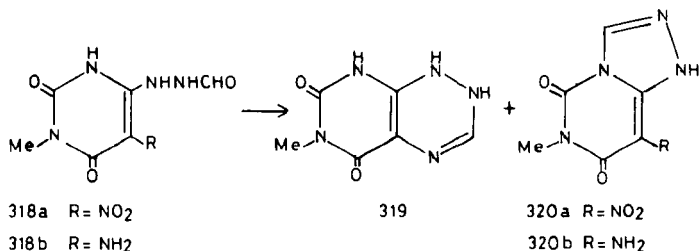
SCHEME 74

The cyclization of aminoformylhydrazinouracil **318b**, derived from the corresponding nitro derivative **318a** by catalytic hydrogenation, gave (87JHC1373) the pyrimido[5,4-*e*][1,2,4]triazine **319** in addition to the triazolo[4,3-*c*]pyrimidine **320b**. The latter was formed via cyclization of **318a** toward the ring nitrogen atom prior to reduction of the nitro functionality to afford **320a**, which then underwent hydrogenation to give **320b**.

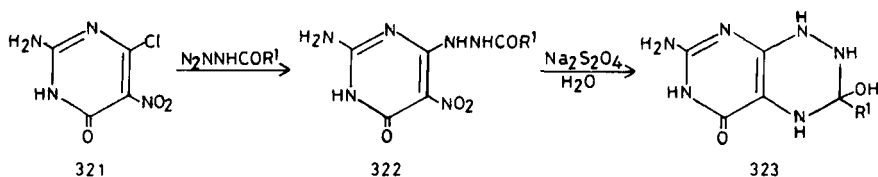
The hydrated dihydropyrimidotriazines **323** were prepared from the pyrimidine **321** by sequential amination and cyclization or by sequential amination, acylation, and cyclization [80JCR(S)278]. Thus, acylhydrazines reacted with pyrimidine **321** to give acylhydrazinopyrimidines **322**, which then were cyclized by treatment with aqueous sodium hydrosulfite to give **323**. They were found to be inactive as enzyme inhibitors.

The synthesis of xanthothricin (toxoflavin) has been conveniently achieved by starting with the chlorination of 6-hydroxy-3-methyl-2-methylthio-4(3*H*)-pyrimidinone **324** with POCl_3 -DMA to give the chloro derivative **325**, which underwent acidic hydrolysis to give **326**. Its nitration produced **327**, which was converted into the formamide derivative **328** by reduction of the nitro group, followed by reaction with formic-acetic anhydride. Reaction of **328** with methylhydrazine gave (87JHC1373) 1,6-dimethylpyrimido[5,4-*e*][1,2,4]triazine-5,7(1*H*,6*H*)-dione **308**. Demethylation to reumycin **311** was affected by heating in DMF.

Hydrazinolysis of 5-amino-4,6-dichloropyrimidine derivatives with hydrazine hydrate gave the *o*-aminohydrazino pyrimidine **329**, which was cyclized with triethyl *ortho*-formate or acetic acid to give the pyrimidotriazine **330** (73GEP2233242; 74JOC2866). Alternatively, **330** could be prepared from the respective hydroxy analogue by the action of phosphorus oxychloride (75JOC2321). Compound **330** undergoes nucleophilic displacements of the chlorine atom [74JCS(PI)1565; 75JOC2321; 78JOC469; 81KFZ50; 82JHC1309]. Thus, amination of the latter with various amines afforded **331** (73GEP2233242). Nucleophilic attack of the furazanopyrimidine by acylhydrazides also gave **331** (73JOC2238). Cyclization of the *o*-



SCHEME 75

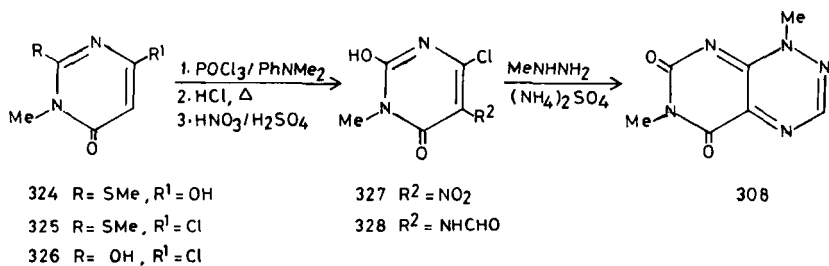


SCHEME 76

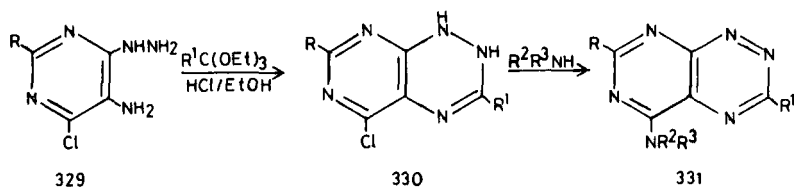
nitrohydrazinopyrimidine derivatives was effected by formation of a Schiff base derivative followed by reductive cyclization and oxidation to give the pyrimidotriazine ring [73AJC1689; 74AJC1781].

When 5-methoxypyrimido[5,4-*e*][1,2,4]triazine or **330** was dissolved in liquid ammonia they quickly were converted (87JHC1657) into 5-aminopyrimido[5,4-*e*][1,2,4]triazine. Pyrimido[5,4-*e*][1,2,4]triazin-(6*H*)-5-one was also present in the product mixture from **330** ($R=H$) and its formation was explained by the presence of water in the hygroscopic hydrochloride. When **330** ($R=H$) was kept in liquid ammonia containing an excess of potassium permanganate, 3,5-diaminopyrimido[5,4-*e*][1,2,4]triazine was formed. Reaction of 5-(benzylthio)pyrimido[4,5-*e*][1,2,4]triazine with benzylamine in isopropyl alcohol gave (85USP4494981) the 5-*N*-benzyl derivative of **330** which controlled barnyard grass and garden cress. The preemergence activity of the 5-methoxy analogue of **330** was determined with respect to certain species of crop plants. Amines **331** have antiinflammatory activity and are useful as diuretics (73GEP2233242; 74USP3813393).

Condensation of **332** with ethyl *ortho*(ethoxycarbonyl)-acetate gave **337** via the air oxidation of **333**; bromination of its methylene group was unsuccessful. On the other hand, reaction of **332** with *ortho*(chloro)acetate gave **334** and **336** (75JOC2205). Oxidation of **334** with silver oxide gave 7-azaaminopterin **337**, a potential inhibitor of dihydrofolic reductase. Ring



SCHEME 77

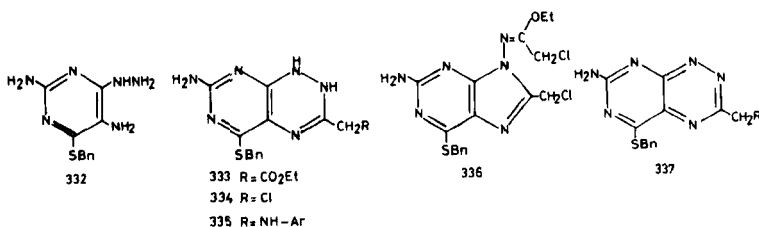


SCHEME 78

closure of **332** with an *N*-carbonitrilomethylaniline or the respective imino-ether gave **335**, which is inactive against malarial infection in mice and L1210 leukemia *in vitro* (73JHC889; 85JHC1369). Displacement of the benzylthio group of **337** with azide anion followed by reduction gave the corresponding amine.

The antibiotic 2-methylfervenulone (**310**) was synthesized most conveniently by treatment of **338** with dimethylformamide–phosphorus oxychloride to afford **339**, followed by acid hydrolysis to give fervenulone **340**. Subsequent alkylation with methyl iodide in dimethylformamide gave **310** (78JOC469). Reaction of **339** with sodium benzyloxide gave the benzyloxy derivative **344**, which on catalytic reduction with palladium–charcoal provided **340**.

The fervenulin 4-oxide **342** ($R = H$) was synthesized (77H273, 77JHC175; 78JOC469) in a single step by the reaction of 6-hydrazino-1,3-dimethyl-5-nitrosouracil (**338**) with a one-carbon reagent such as dimethylformamide–phosphorus oxychloride, dimethylformamide–dimethyl sulfate, formic acid, or triethyl orthoformate. Compound **342** was found to be a versatile intermediate for the synthesis of the antibiotic fervenulin **309** on treatment with sodium hydrosulfite in water. Cyclization of 6-amino-1,3-dimethyl-5-nitrosouracil with aldehydes and hydrazine also gave fervenulins **341** (73CPB448; 74JHC83; 75BCJ2884, 75CPB1885; 76CC658; 84JHC969). The cyclization of **338** was also effected by the reaction with tetrahydrothiopyran-3-aldehyde to give **342**, a herbicide (91EUP407888).



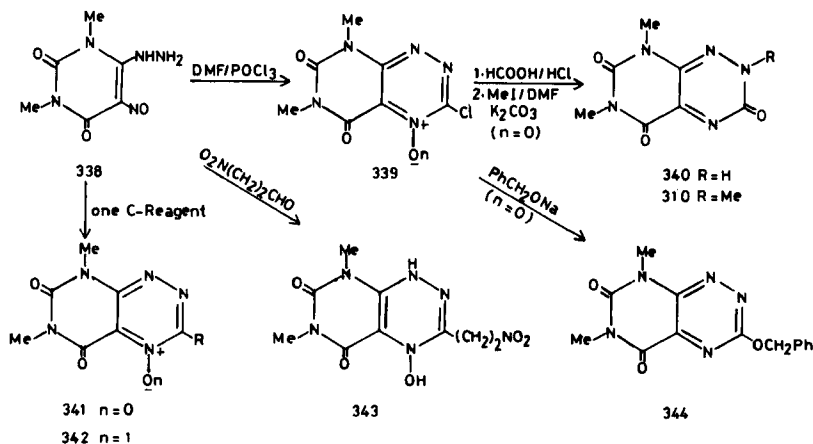
SCHEME 79

Reaction of **338** with *ortho*-esters afforded the corresponding 3-substituted fervenulin 4-oxide **342** (78JOC469).

3-Arylfervenulins (**341**) were prepared by treatment of **338** with disubstituted benzyl halides in dimethyl sulfoxide (77H1921), or benzylidenetriphenylphosphoranes (78H29), or phenacyl bromide in dimethyl sulfoxide (77H1921), or acetophenone (76CPB1917). Nitrosative cyclization of 1,3-dimethyl-6-(α -benzalhydrazino) uracil with *N*-nitrosodimethylamine and phosphorus oxychloride also afforded **341** (R = Ar) (76CPB1917). On the other hand, cyclization of **338** with 3-nitropropionaldehyde or *p*-(*N,N*-dichloroethylamino)benzaldehyde gave the pyrimidotriazines **343** and **341** (R = Ar), respectively (84KFZ573). Compounds **341** and **342** had herbicidal activity.

Magnetic circular dichroism spectra of some 3-arylfervenulins and 3-aryltoxoflavins were studied (78JHC615). Hammett plots showed that substituents in both compounds exerted opposite effects on the magnetic CD spectra. The difference was explained by the contribution of the 1,5-dipolar structure of 3-aryltoxoflavins.

The reaction of 6-hydrazino-1,3-dimethyluracil **345** with triethyl *ortho*-formate gave 6-ethoxymethylenehydrazino-1,3-dimethyluracil **346**, whose treatment with arylamines gave **347**, which then underwent cyclization with nitrous acid to give (82JHC1309) the pyrimido[5,4-*e*][1,2,4]triazin-4-oxides **350**. The reaction proceeds via the initial formation of 5-nitrosouracil **348** followed by cyclization to the cyclic hydroxylamine **349** and subsequent dehydrogenation with excess nitrous acid. Reduction of **350** with sodium dithionite to remove an oxygen atom gave **351**, which

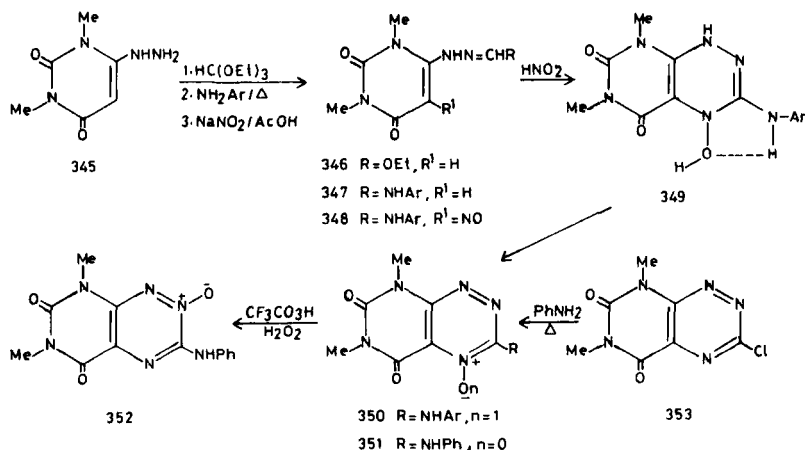


SCHEME 80

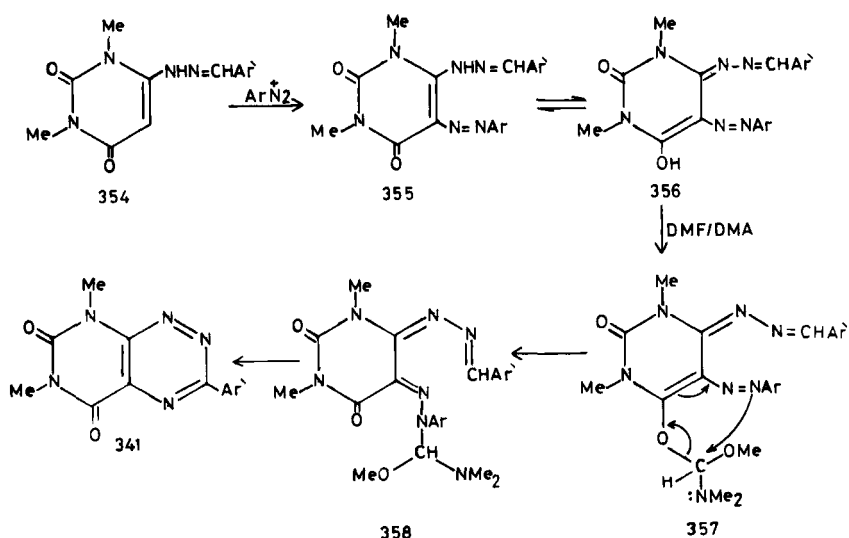
was also obtained by reaction of **353** with aniline. Oxidation of **351** with trifluoroperacetic acid gave the 2-oxide **352**.

The construction of this ring system also proceeded from 5-aryldio-6-arylidenehydrazino-1,3-dimethyluracils **355** that were readily prepared by reaction of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils **354** with diazotized arylamines. Their treatment with dimethylformamide-dimethylacetal (DMFDMA) gave (81H559; 82JHC769) 6,8-dimethyl-3-arylfervenuin **341** via the intermediates **357** and **358**. The yields depended on the nature of the arylidenehydrazino group of **355**; those with electron-withdrawing groups gave better results than those with electron-releasing ones. Also, compounds **354** can be cyclized by potassium nitrate and acetic acid to give the 4-oxides of **341** (76CPB338).

Acetylation of 2-amino-4-hydrazino-6(1*H*)-pyrimidone **359** gave the acetyl derivative **360**, which was subjected to Michael addition with diethyl azodicarboxylate (DEAD) to give **362**. Its treatment with sodium ethoxide gave **366** (79JOC1125). Reaction of 2-amino-4-(1-methylhydrazino)-6(1*H*)-pyrimidone with acetic anhydride followed by DEAD gave **363**, which on treatment with sodium ethoxide gave **366**. However, reaction of 2-amino-4-(1,2-dimethylhydrazino)-6(1*H*)-pyrimidone **361** with DEAD gave the Michael adduct **364**, but all attempts to effect its cyclization failed. On the other hand, **365** gave **367** under similar treatment. Cyclization of 5-(1,2-dicarbethoxyhydrazino)-6-(2-formylhydrazino)-1,3-dimethyluracil was similarly effected to give the corresponding pyrimido[5,4-*e*][1,2,4]triazine **340** (75JOC2321). Reaction of 6-(2-benzylidene-1-methylhydrazino)-3-



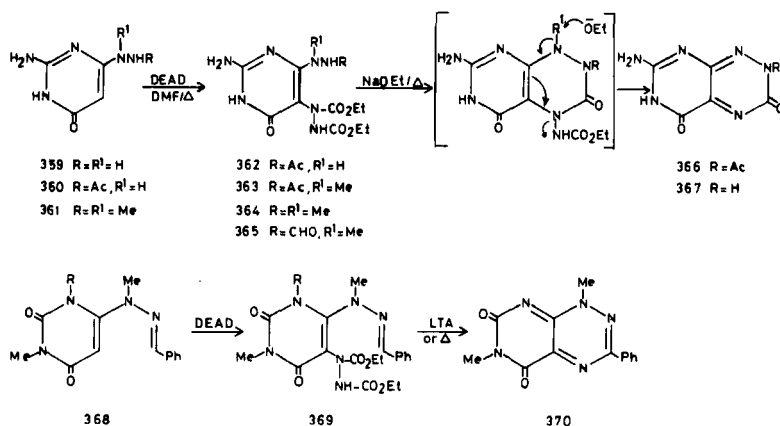
SCHEME 81



SCHEME 82

methyluracils **368** with DEAD gave **369**, which with $\text{Pb}(\text{OAc})_4$ cyclized to **370** or **342** [76JCS(PI)2398].

A new synthesis of fervenulins **341** in a single step was developed (77JA7358; 78JA7661) by the photolysis of 6-azido-1,3-dimethyluracil **372** in the presence of acylhydrazines. Their reaction could not be effected by heating, suggesting that photochemical activation is required. Thermol-



SCHEME 83

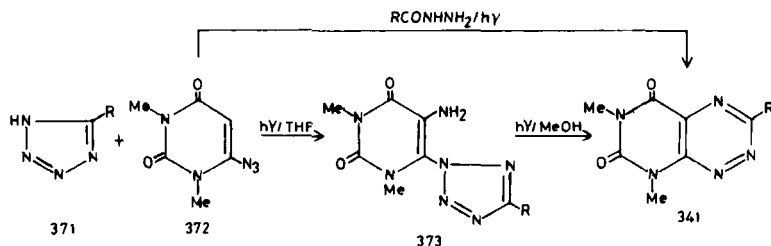
ysis of **372** with tetrazoles **371** afforded **341** (81H285), whereas photolysis in THF gave **373**, which on further photolysis in MeOH gave **341**. The latter was also obtained by thermolysis of **373**.

The synthesis of the *lin*-benzo-separated analogue **380** of the broad spectrum antibiotic fervenulin was reported (81JOC1699) in five steps from 7-chloro-2,4(1*H*,3*H*)quinazolin-2-one **374**. Nitration of **374** gave **375**, whose methylation gave **376**. Pursuant to the synthesis of **380**, **376** was converted into **377** with hydrazine and then formylated with formic acid to give **378** or converted to the ethoxymethylene derivative **379**. Catalytic hydrogenation of **378** or preferably **379** gave **380**.

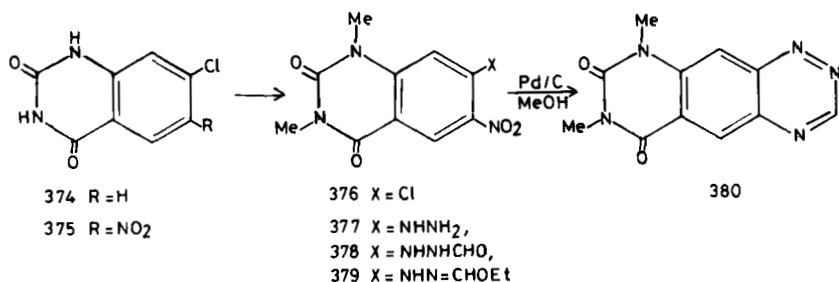
When the reaction of diethyl oxomalonate **381** was carried out with the free *S*-methyl isothiosemicarbazide, triazine **281** was obtained in addition to its isomeric triazine **382**. Reaction of **382** with phosphorus oxychloride gave **383**, whose reaction with guanidine or benzamidine gave **384**, which cyclized to **385**. This represents (85JOC2293) the first example of a preparation of this bicyclic system from a 1,2,4-triazine.

Thermolysis of 7-amino-6-azido-1,3-dimethylxanthine (**386**) in chlorobenzene gave 3-aminofervenulin (**387**) through a nitrene intermediate (92MI1). 7-Aminotheophylline **388** and **389** were oxidized by various oxidizing agents to give **309** and **311**, respectively (89KGS95).

The antibiotic reumycin (**311**) was prepared in almost quantitative yield by the selective dealkylation of xanthothricin **308** or its analogues with nucleophilic solvents such as dimethylformamide (73JA5735; 75CPB2001) or better by secondary amines such as diethylamine [80BRP2039883, 80GEP2901537, 80JAP(K)80102580] followed by acidification with acetic acid. The use of acetone as a solvent resulted in a lower yield of **311** owing to the formation of the adduct **390** (88MI1). Demethylation of xanthothricin was carried out also with alkali to give reumycin (81URP558533). On the other hand, reaction of fervenulin **309** with a 90-fold molar excess of diethylamine gave pyrido[3,2-*d*]pyrimidinedione **391** and uracil derivatives **392** (89KGS274; 90KGS224). Catalytic hydrogenation-



SCHEME 84

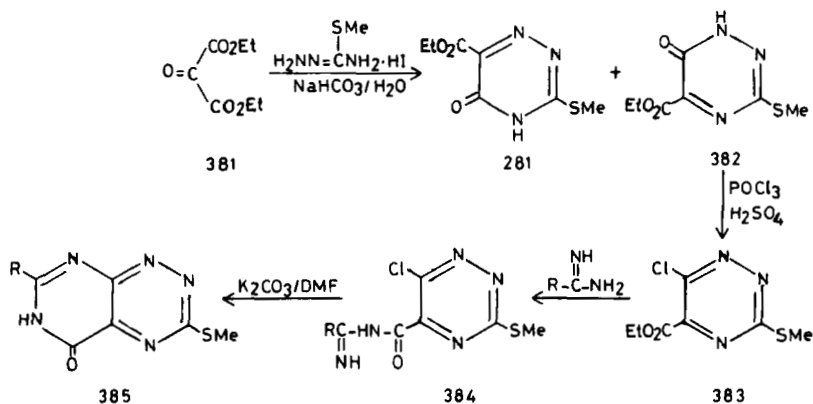


SCHEME 85

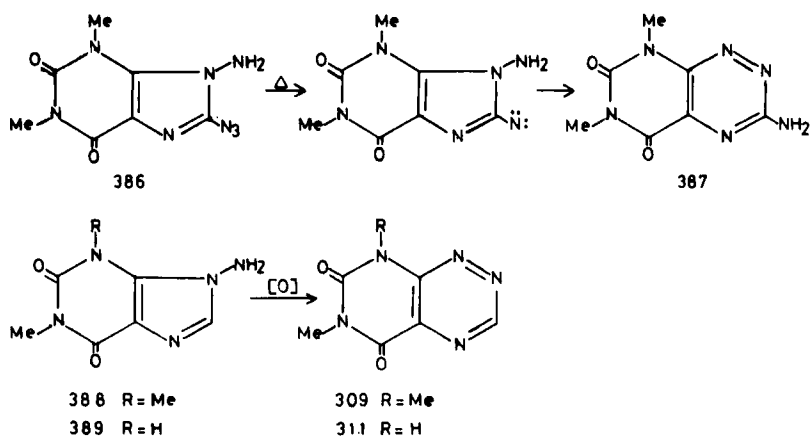
tion of reumycin over platinum oxide in acetic anhydride gave acetyl derivatives **393–397** (81KPS85).

Reaction of fervenulin oxide **342** (R = H) with 2-methylindole in aqueous ethanol containing *p*-nitrobenzaldehyde gave 3-(*p*-nitrophenyl)fervenulin **398** and the pyrimidinedione hydrazone **399**, whereas treatment of **342** with indole gave only **398** (85KGS998). Indole and 2-methylindole underwent addition reactions with fervenulin **309** in HCl–EtOH to form **400** (87KPS155; 91KPS110), whose structure was confirmed by X-ray crystallography. A 1 : 1 crystal molecular complex was formed via a charge–transfer interaction of the indole nitrogen with **309** or the 4-oxide **340** in boiling butanol to give **401** (85KGS998; 86KGS563).

Heating of aryltoxoflavines **313** or arylfervenulins **314** with formamide resulted in a cleavage of the triazine ring to give **402** (76H749). On the other hand, when the triazine ring is stable, opening of the pyrimidine



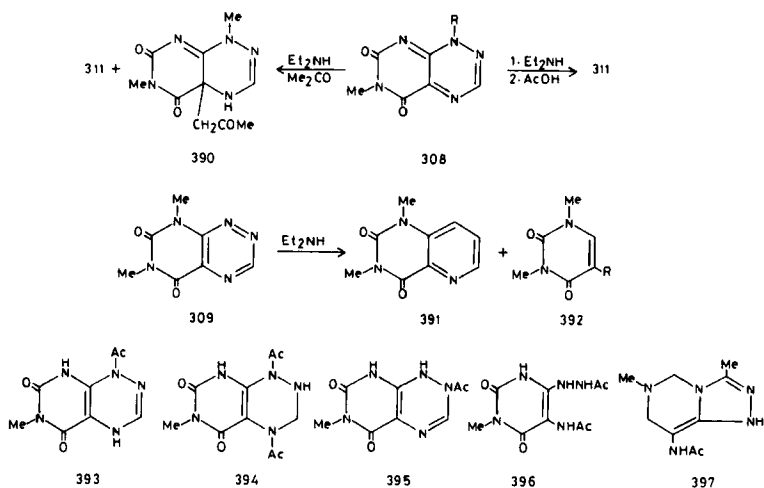
SCHEME 86



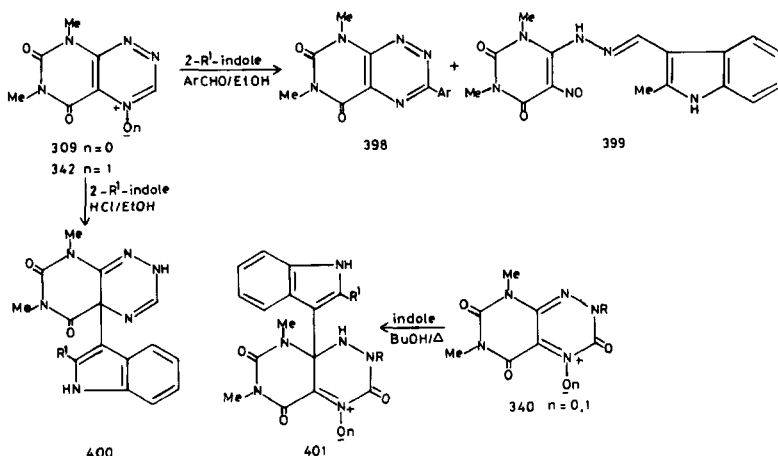
SCHEME 87

ring could be effected to give azapurine analogues by the action of alcoholic sodium hydroxide (78CPB3154; 80JHC869; 85KGS277). Alkylation of **313** was accompanied by an unusual methylation to give **314** (73TL1577; 74JHC271; 75BCJ2884, 75MI1; 86MI4).

The reaction of **341** (R = H, OH) with 1,3-dimethyl-6-hydrazinouracil **345** in ethanol containing hydrochloric acid gave **403**. Its removal from the



SCHEME 88



SCHEME 89

mother liquor, followed by concentration, gave the starting adduct and barbituric acid **404** (88KPS312).

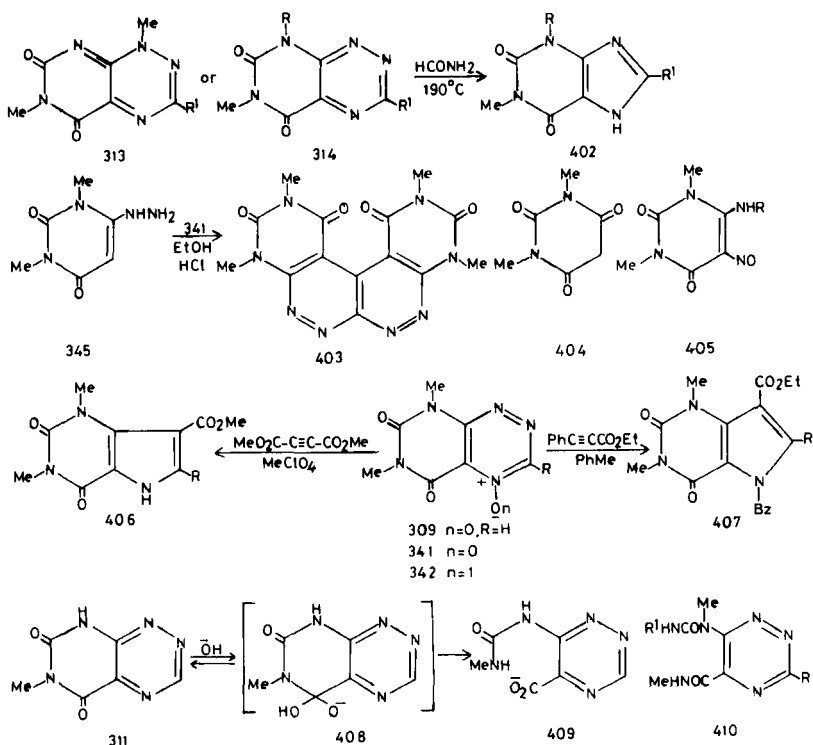
Fervenulin 4-oxide **342** reacted with acids, amines, acetoacetate, and acetylacetone to give ring cleavage products **405** (84KGS1692; 85KFZ1202; 86KFZ1228; 91MI4). Changing the condition of reactions may afford different products such as 6-hydroxypyrimidine derivatives.

1,3-Dipolar cycloaddition reaction of fervenulin-4-oxides **342** with dimethyl acetylenedicarboxylate or methyl propiolate gave a variety of pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) **406** (78H793; 79JOC3830; 82JHC1309). On the other hand, the reaction of pyrimidotriazine derivative **341** with carbethoxyphenylacetylene gave the pyrrolopyrimidine **407** (85JOC2413).

A kinetic study of alkaline hydrolysis of reumycin **311** indicated that OH^- added reversibly to C-5 to form an intermediate **408**, which then decomposed to the triazine **409** (88MI2). At high OH^- concentrations, the rate-limiting step was the attack of OH^- on C-5 of **311**, whereas at low OH^- concentrations it was the cleavage of the uracil ring in intermediate **408**.

Reaction of fervenulins **309** and **341** with alkylamine gave ureidotriazine **410** by pyrimidine ring cleavage. *N,N*-Dimethylhydrazine and hydrazine reacted similarly to give triazinylsemicarbazides, but, when compound **309** reacted with methylhydrazine, a preferential cleavage of the triazine ring took place [74JCS(P1)1818].

Reumycin **311** was silylated with $F_3CC(=N-SiMe_3)-OSiMe_3$ to give **411**, which was glycosylated with tetra-*O*-acetyl- β -D-ribofuranose **412** to



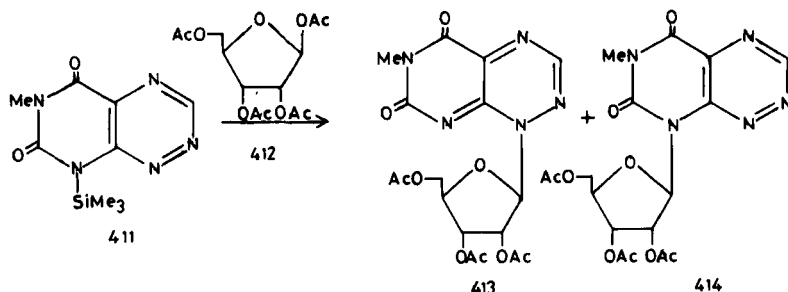
SCHEME 90

give a mixture of **413** and **414**. The reaction could be extended to the 2-deoxy and the glycopyranosyl derivatives (81MI4).

Treating glycosyl isothiocyanates **415** with 5,6-diamino-1,3-dimethyluracil (**416**) gave thioureas **417**, which on oxidative cyclization with *N*-bromosuccinimide afforded 5,7-dioxypyrimido[5,4-*e*][1,2,4]triazine nucleosides **418** (80MI1; 82MI2).

Pyrimido[5,4-*e*][1,2,4]triazinediones in aqueous acidic media were hydrated at the N4-C4a bond to give covalent hydrates; the structures of which were confirmed by X-ray analysis. The products of hydrate decomposition in acidic media were formic acid, 5-diazo-3-methylbarbituric acid, and methylparabanic acid (88KGS1654).

The stability of reumycin, fervenulin, and xanthothricin in acid-base media was studied by ^1H - and ^{13}C -NMR spectroscopy (85MI1). Infrared and absorption spectra of reumycin **311** were studied at low temperature (87MI2). The experimental data corresponded to the quantum chemical calculations of electron transmission. The pK_a of **311** in aqueous medium



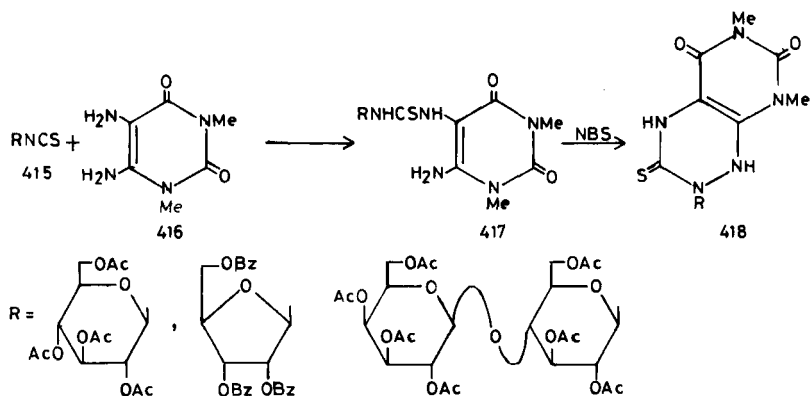
SCHEME 91

was determined by UV spectrometry. A spectrophotometric method is described for the determination of toxoflavin in toxic metabolites (91MI8).

The radical anions of **309**, **311** (Me derivative of enol), and **308** were generated electrochemically; ESR spectroscopy indicated that the unpaired electron was delocalized in the triazine moiety (81MI3).

The mass spectra of a series of ring systems were examined by the DADI technique. The primary fragmentation produced a $[M-28]^+$ species in the case of **309** and **311** (Me enol), which resulted from the loss of N₂, whereas in the case of **308**, it resulted from loss of CO (79KGS1270). Ionization and appearance potentials were also determined.

Xanthothricin **308** stimulated oxidation of NADH and NAD-linked substrates by rat liver mitochondria, yeast mitochondria, and Ehrlich ascites tumor cells (74MI1, 74MI3). It also stimulated mitochondrial oxidation of succinate, pyruvate, or malate. The antibiotic xanthothricin was obtained



SCHEME 92

by aerobic fermentation of *Streptomycin brunneus* subspecies *xanthothricini* RIA 1568 (80BRP2040281).

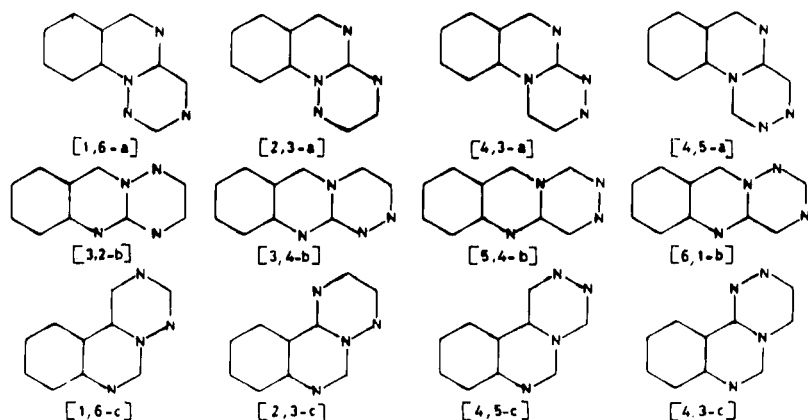
Reumycin and xanthothricin were isolated from *Actinomyces rectus brunneus* and are useful as antitumor antibiotics. Methylation of reumycin resulted in the formation of the antibiotics, fervenulin, toxoflavine, and 7-methoxyreumycin. A review on their effects on an electron transport mechanism in animal and yeast cells was published in 1975 by Russian authors (75MI1, 75MI2).

The antibiotic reumycin and variamycin showed activity against carcinoma, melanoma, and carcinosarcoma, but not leukemia (81MI1). Reumycin was found to be cytostatic [80BRP2039883, 80GEP2901537, 80JAP(K)80102580]. Side effects of reumycin were studied in cats, rats, rabbits, and dogs (76MI3). In both dogs and rats prolonged administration decreased the thrombocyte count; in rats it also caused hemoglobinemia without erythropenia. Reumycin was an autooxidizable electron acceptor on the oversynthesis of intermediates by the bacterium *Pseudomonas aeruginosa* during growth under nitrogen (91MI2).

Toxoflavin reduced the respiratory oxygen consumption of mitochondria and suppressed the oxidative phosphorylation activity (91MI1).

7. [1,2,4]Triazino[x,y-z]quinazolines

There are 12 isomeric structures for this ring system, where the triazine ring is directly fused to the pyrimidine nucleus of the quinazoline ring; one of the nitrogen atoms of the quinazoline ring is located at the bridgehead of the bicyclic ring.



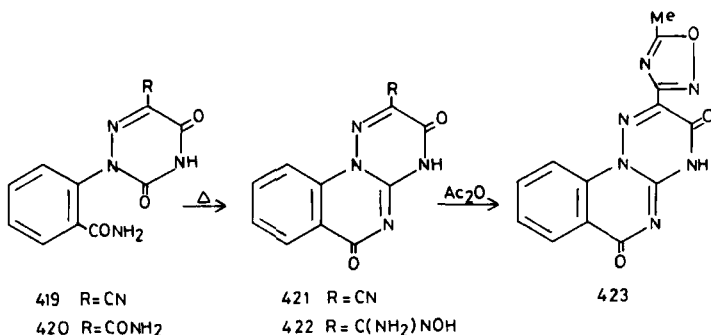
SCHEME 93

a. *[1,2,4]Triazino[2,3-*a*]quinazolines*. Ring system **421** was prepared by thermal cyclization of **419** or **420** (74JPR943). Reaction of **421** with hydroxylamine gave the amidoxime **422**, which was cyclized with acetic anhydride to 1,2,4-oxadiazolyl derivative **423**.

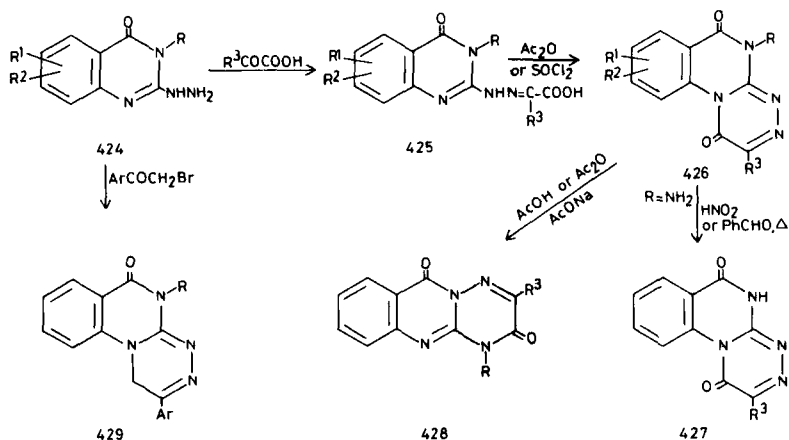
b. *[1,2,4]Triazino[4,3-*a*]quinazolines*. Hydrazinoquinazolines **424**, having various substituents, gave on reaction with pyruvic acid, hydrazones **425**, which undergo cyclization (83GEP160343; 84PHA717; 90JOC344; 94IJCip; 94MIip) by thionyl chloride or acetic anhydride to give selectively 1,6-dioxo-5,6-dihydro-1*H*-[1,2,4]triazino[4,3-*a*]quinazolines **426**. On the other hand, rearrangement of **426** to the isomeric triazino[3,2-*a*]quinazolines **428** was carried out by heating in acetic acid or acetic anhydride in presence of sodium acetate (94IJCip; 94MIip); however, this rearrangement was not realized before (90JOC344). Deamination of **426** with nitrous acid or thermolysis of its benzylidene derivative resulted in the selective synthesis of triazino[4,3-*a*]quinazolines **427**. Antihistaminic and blood platelet aggregation inhibition of **426** were reported.

Cyclization of the hydrazinoquinazolines **424** was also effected (91MI5, 91MI7) by reaction with 4-substituted phenacyl bromides to give [1,2,4]triazino[4,3-*a*]quinazolines **429**.

c. *[1,2,4]Triazino[3,2-*b*]quinazolines*. Triazino[3,2-*b*]quinazolines **431** were prepared (84CB1077, 84CB1083) by cyclocondensation of **430** with anthranilic acid. Condensation of **432** with anthranilic acid gave **433**, whose deamination gave **431**. The reaction of the *N*-benzylidene derivative **434** with anthranilic acid gave **431** with extrusion of cyanobenzene. The *N*-methyl derivative **435** was similarly prepared by the reaction of **430** with *N*-methyl anthranilic acid.



SCHEME 94

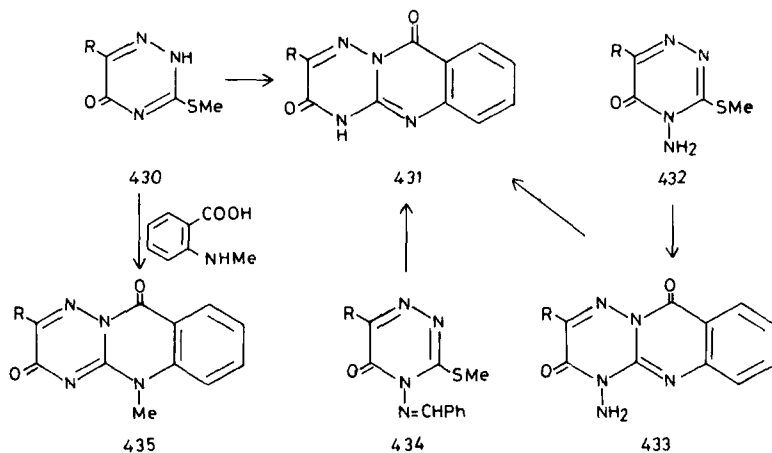


SCHEME 95

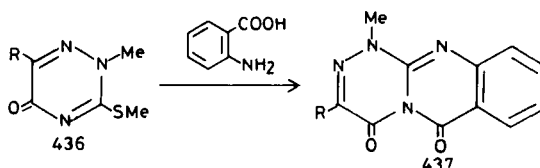
d. *[1,2,4]Triazino[3,4-b]quinazolines*. Using the same type of reaction just described, condensation of *N*-methyl derivative **436** with anthranilic acid gave **437** (84CB1077).

The triazinoquinazolines **439** were prepared (88GEP263061) by cyclocondensation of hydrazinoquinazoline **438** with chloroacetic acid in toluene.

Related to this ring system is [1,2,4]triazino[4,3-*a*]perimidine where the same face of the triazine again is involved in ring fusion. Heating



SCHEME 96



SCHEME 97

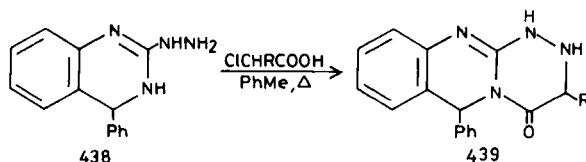
2-hydrazinoperimidine derivative **440** with ethyl pyruvate afforded 3-methyl[1,2,4]triazino[4,3-*a*]perimidin-4(1*H*)-one **442** via the hydrazone intermediate **441** (85JHC1363). However, cyclocondensation of **440** with diethyl oxalate gave 1*H*-[1,2,4]triazolo[4,3-*a*]perimidine-3-carboxylate **443** instead of the expected 1,2-dihydro-[1,2,4]triazino[4,3-*a*]perimidine-3,4-dione **445** via **444**.

Another example of this ring system is found in tetracyclic triazinoperimidines **447**. They were prepared by treating perimidinium salts **446** with hydrazine hydrate to give **447**, which then were oxidized with $\text{Ph}_3\text{C}^+\text{ClO}_4^-$ to give triazinoperimidinium perchlorates **448** (86KGS1389).

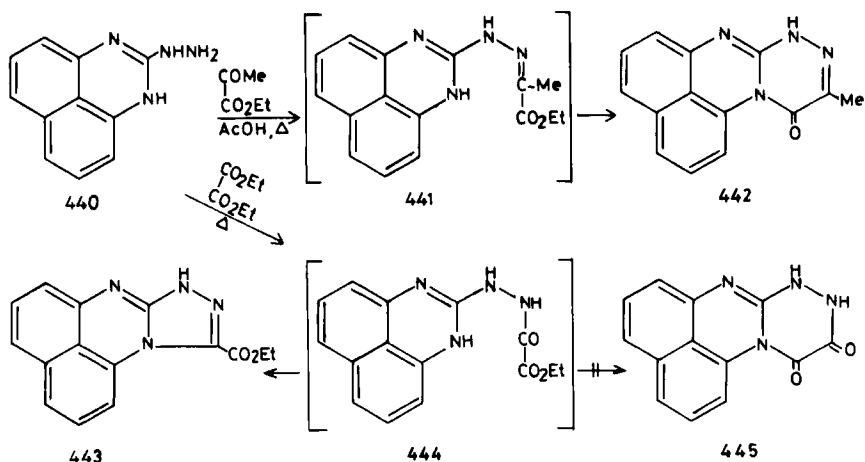
e. [1,2,4]Triazino[6,1-*b*]quinazolines. Cyclization with alkyl cyanides of a quinazolone **449**, having *o*-amino ester groups, [90IJC(B)174] gave **450**. However, reaction of **449** with various alkyl-amines in methanol gave amides that reacted [90IJC(B)174, 90SC23] with *ortho*-esters to give [1,2,4]triazino[6,1-*b*]quinazolin-4,10-diones **452**. Reaction of ester or amide **449** with isocyanates or thiocyanates gave the respective products **451** [92IJC(B)193].

The reaction of 3-isonitrosopyrazolo[5,1-*b*]quinazolin-2,9-dione **453** with the Vilsmeier reagent gave the expected *o*-cyanoamidine derivative, which was cyclized [77IJC(B)335] by hydroxylamine to [1,2,4]triazino[6,1-*b*]quinazolin-10-one **454**.

f. [1,2,4]Triazino[1,6-*c*]quinazolines. Methylation of 7-acetyl-6,7-dihydro derivative **456**, obtained by condensation of the triazinone **455** with oxo compounds and then acetylation, gave the corresponding methio-



SCHEME 98

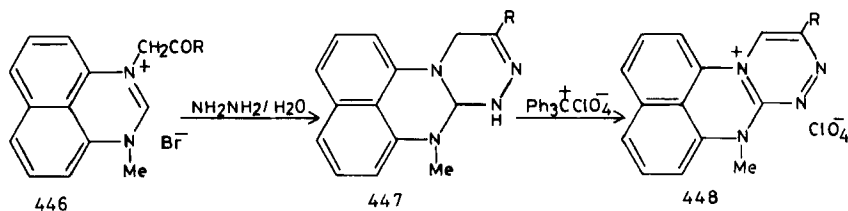


SCHEME 99

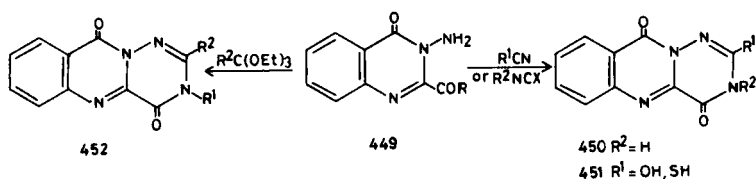
dide **457**. Degradation of **457** by sodium hydrogen sulfite afforded pseudobase **458**. Treatment of the pseudobase with potassium iodide in acetic acid converted it into **457**. Reduction of **457** with sodium borohydride furnished the corresponding compounds **459** (76T1735). Condensation of **455** with aroyl chlorides gave **460** where a similar series of conversions was carried out. The triazine precursor **455** may be considered to be a trapping agent for aldehydes via the reaction to **456** (76ACH419).

The crystal and molecular structures of 6,6-dimethyl-3-methylthio-6,7-dihydro[1,2,4]triazino[1,6-*c*]quinazolin-5-ium-1-olate **461**, obtained by condensation of **455** with acetone, confirmed its zwitterionic structure (75CSC295). Analogues of **461** were also prepared for thermolysis studies (74T3997).

C-Nucleoside analogue **464** of this ring system was prepared (86SC35) from 2,5-anhydro-3,4,6-tri-*O*-benzoyl-L-mannose dimethyl acetal **462** and 6-(2-aminophenyl)-3-methylthiotriazin-5(2*H*)-one **463** in the presence of acetic and hydrochloric acids.



SCHEME 100

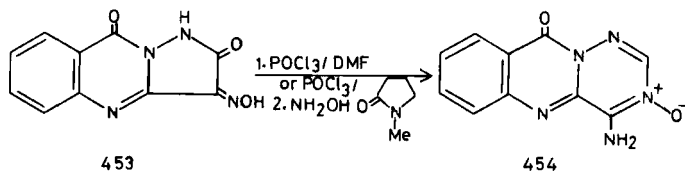


SCHEME 101

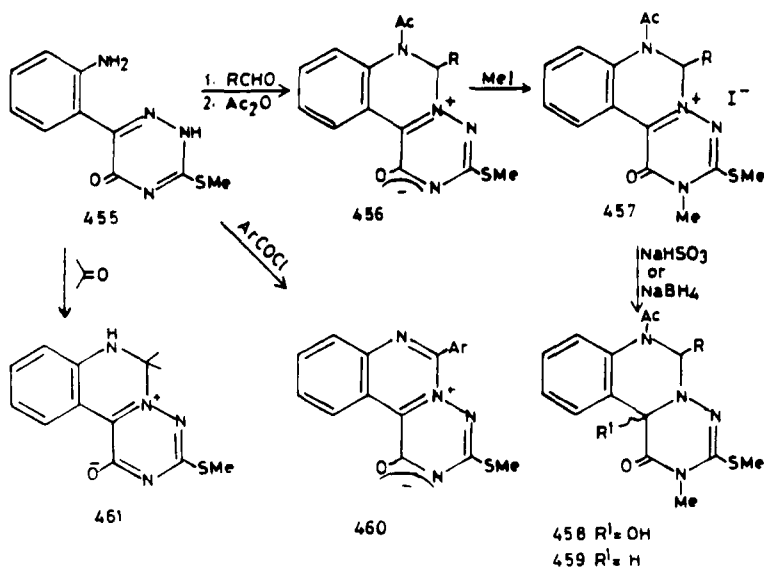
g. [1,2,4]Triazino[2,3-*c*]quinazolines. Heating 3-*o*-aminophenyltriazine **465** with polyphosphoric acid at 100°C or at 200°C led to the formation of **466** and **467**, respectively (74JHC747).

h. [1,2,4]Triazino[4,3-*c*]quinazolines. The triazine **468** was cyclized (75JHC321) with various reagents to give this ring system. Thus, the triazinoquinazolines **471** were obtained from **468** by reaction with aldehydes and ketones. The acyl derivatives **470** were cyclized thermally to **472**. This thermal cyclodehydration was retarded by the presence of *ortho* substituents on the benzoylamino moiety of **470**. The reaction of **468** with isocyanates gave ureas **469**, which were thermally cyclized to **467**. Compound **467** was also prepared from **468** by reaction with phosgene and ethyl chloroformate. The triazinoquinazoline **467** was also prepared (74JHC747) from 2-oxo-4-thiono-1,2,3,4-tetrahydroquinazolidinedione **473** on treating with hydrazine derivative **474** to give **475** (R = OH), followed by chlorination and cyclization.

The triazine ring could be formed by reaction [82S853; 83BSF(2)226] of alkyl (2-aryl-4-thioxo-3,4-dihydro-2*H*-quinazolin-3-yl)acetates **477**, prepared from **476**, with hydrazine to yield 6-aryl-2,4-dihydro[1,2,4]triazino[4,3-*c*]quinazolin-3-ones **478**.



SCHEME 102



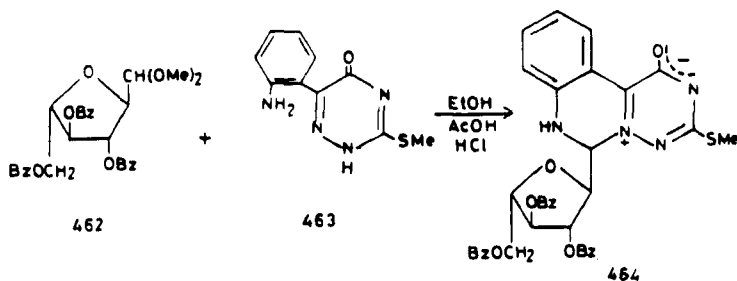
SCHEME 103

C. [1,4]DIAZINO[x,y-z][1,2,4]TRIAZINES

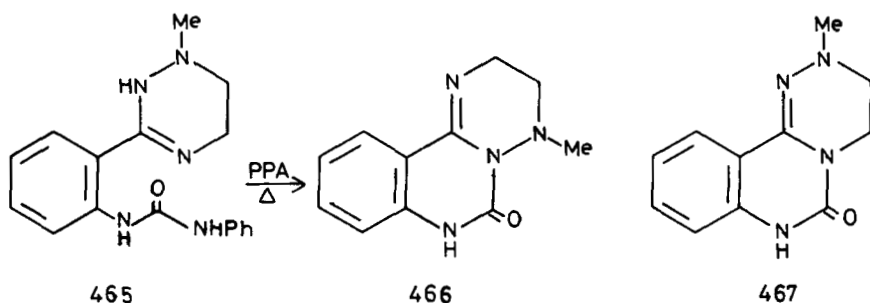
Five isomeric structures are possible for the bicyclic compounds of this ring system, one isomer on each face of the triazine ring, except face *a*, as shown in Scheme 108.

1. *Pyrazino*[2,3-*e*][1,2,4]triazines

The first examples were recently synthesized (86JHC33). Thus, 6,7-dihydroxy-5,6,7,8-tetrahydropyrazino[2,3-*e*][1,2,4]triazines **481** were pre-

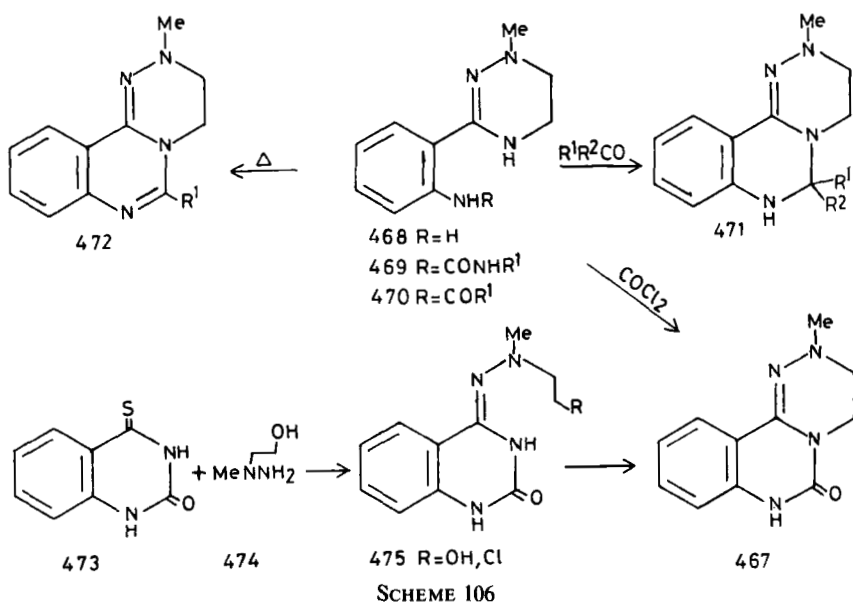


SCHEME 104

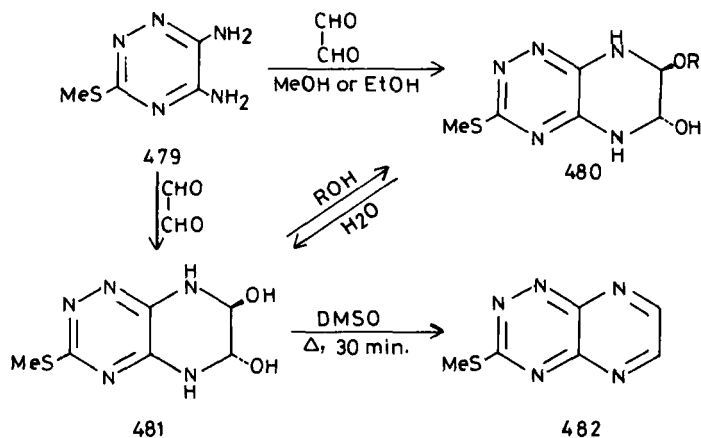


SCHEME 105

pared by ring closure of 5,6-diamino-3-methylthio[1,2,4]triazine **479** with aqueous glyoxal. These 4-azapteridines experience a novel exchange process with alcohols at the C-7 position to give **480**. This adduct was easily converted to **481**. Spectroscopy (NMR) has verified the intermediacy of the *cis* adduct, but because of the exchange process, only the *trans* isomer was isolated. Its structure was determined by a single-crystal X-ray diffraction study. Dehydration of **481** gave **482**.



SCHEME 106



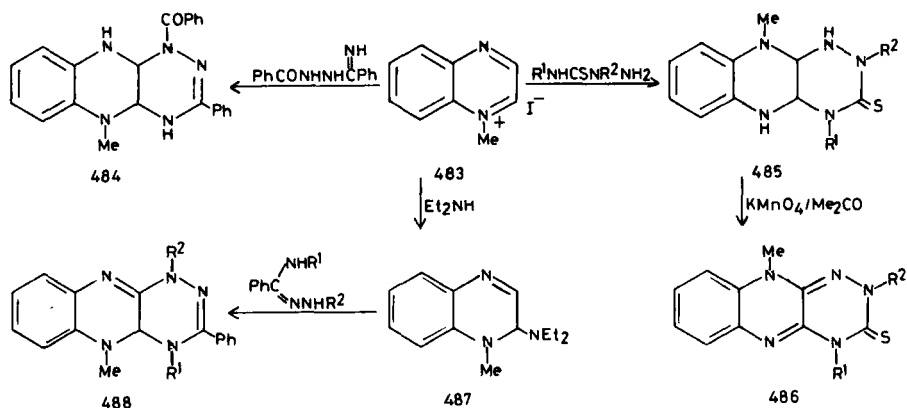
SCHEME 109

V. [1,2,4]Triazino-oxazines

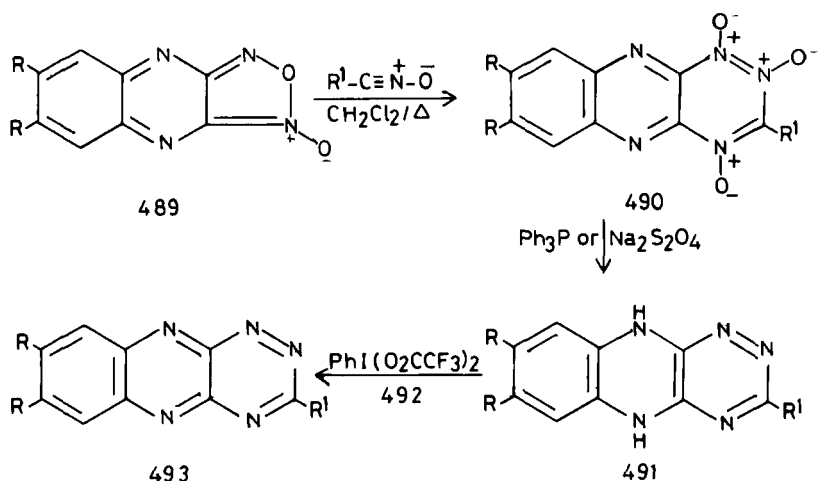
A. [1,2,4]TRIAZINO[*x,y-z*]BENZOXAZINES

1. [1,2,4]Triazino[6,1-*c*][1,4]benzoxazines

Thermolysis of the hydrazone **497** having an azido group, prepared from the respective chloro derivative **496**, in boiling benzene gave 3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-*c*][1,4]benzoxazines **498** [80TL559; 82JCS-(P1)755], whose X-ray structure was studied [83AX(C)605]. The reaction



SCHEME 110



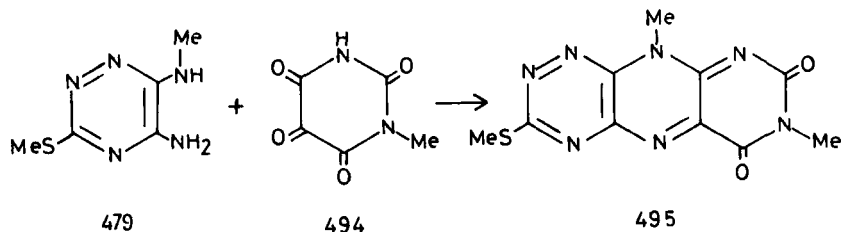
SCHEME 111

involves initial formation of nitrene intermediate followed by intramolecular 1,4-cycloaddition.

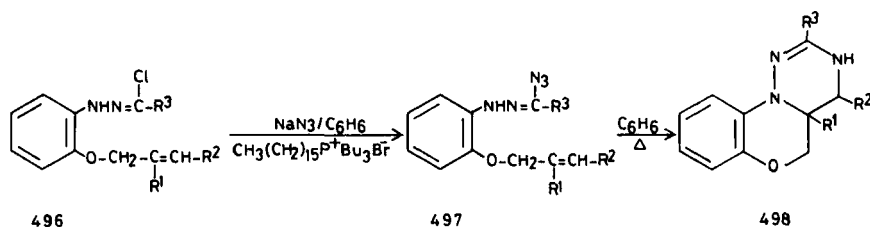
Oxidation of the triazinobenzoxazines **499** by manganese dioxide in chloroform gave **500** and **501**. Saponification of **500** (R = OEt) gave the corresponding acid (89JHC899).

2. [1,2,4]Triazino[3,4-c][1,4]benzoxazines

Heating the hydrazine derivative **502** with ammonium acetate in the presence of acetic acid gave triazinobenzoxazine derivative **503** (88JIC735). Both **502** and **503** exhibited bactericidal activity. Derivatives of the latter had antiinflammatory activity (91MI6).



SCHEME 112



SCHEME 113

VI. [1,2,4]Triazino-thiazines

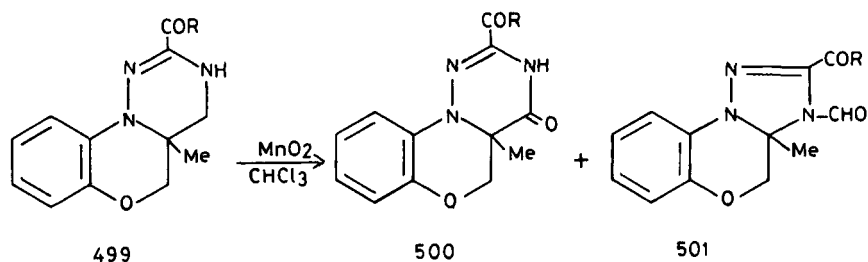
A. [1,2,4]TRIAZINO[*x,y-z*]THIAZINES

1. [1,2,4]Triazino[3,2-b][1,3]thiazines

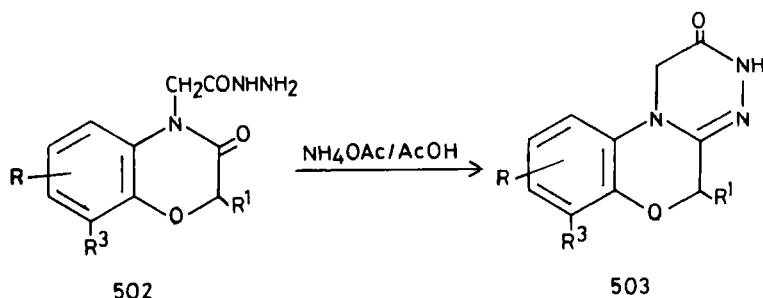
3-(3-Butynylthio)[1,2,4]triazin-5-ones **504** participate in competitive intramolecular Diels–Alder and intramolecular coplanar cycloamination processes to provide triazinones **505**, and pyridinones **506**. In relatively inert aromatic solvent systems, their ratios are markedly dependent on the electronic disposition of the substituent at C-6 of **504** (84H1225; 88JOC5093).

2. [1,2,4]Triazino[3,4-b][1,3]thiazines

Cyclization of 2-hydrazono-5,6-dihydro-4*H*-1,3-thiazine **507** with glyoxalic acid or ester gave the triazino-thiazines **508** (84LA1302).



SCHEME 114



SCHEME 115

3. [1,2,4]Triazino[6,5-*b*][1,4]benzothiazines

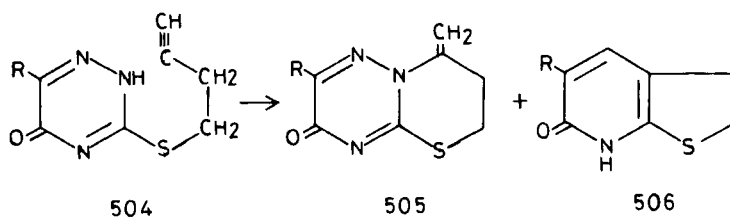
The 4H-benzo[*b*][1,2,4]triazino[6,5-*b*][1,4]thiazin-3(2*H*)-ones **510** were prepared [74JAP(K)7448697] by cyclization of **509** using acetic acid. Derivatives with substituents on the nitrogen of the thiazine ring as in **512** were similarly prepared from **511** [74JAP(K)7448698; 76JAP(K)7605399]. Halogenation of **512** ($R = R^1 = H$) gave **513** [74JAP(K)7448699].

4. [1,2,4]Triazino[3,4-*c*][1,4]benzothiazines

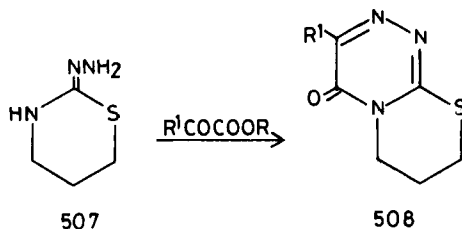
This ring system was prepared by the alkylation of [1,4]benzothiazinone with ethyl bromoacetate followed by reaction with Lawesson's reagent and cyclization with hydrazine to give the thia analogue of **503** (91M16).

5. [1,2,4]Triazino[6,1-*c*][1,4]benzothiazines

The thermal cyclization of *N*-(2-alkenylthiophenyl)-*C*-azidohydrazones **514** gave **515** [84JCR(S)364]. The ring closure proceeds via uncommon 1,2,4-triaza-1,3-diene intermediates.



SCHEME 116



SCHEME 117

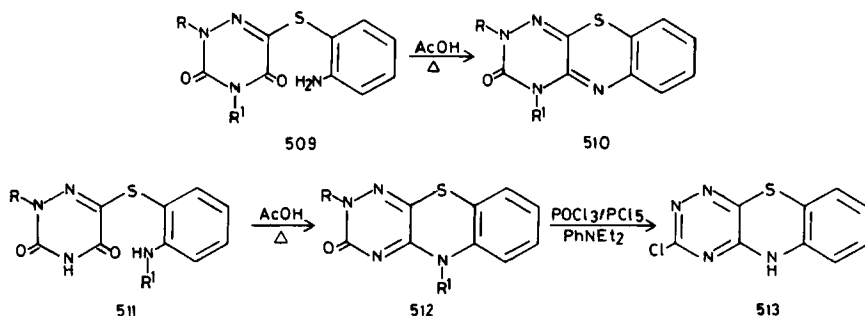
VII. Triazino[1,2,4]triazines

There are three types of triazines that are fused to [1,2,4]triazine parent rings. These are the 1,2,3-, 1,2,4-, and 1,3,5-triazines, and each one is subdivided according to the site of fusion to the parent as indicated by the letter z in the general formulas used below.

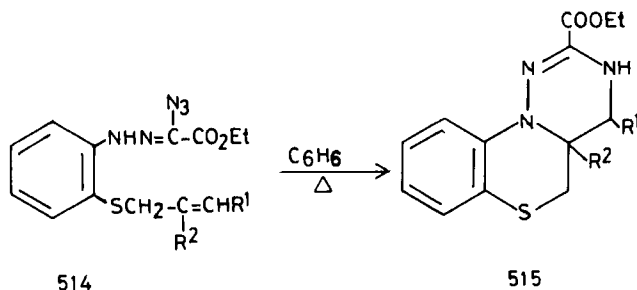
A. [1,2,4]TRIAZINO[x,y-z][1,2,3]TRIAZINES

1. [1,2,4]Triazino[4,3-c]benzo[1,2,3]triazine

The title compound was prepared by the action of nitrous acid on **516** whereby **517** was obtained (75JHC321).



SCHEME 118



SCHEME 119

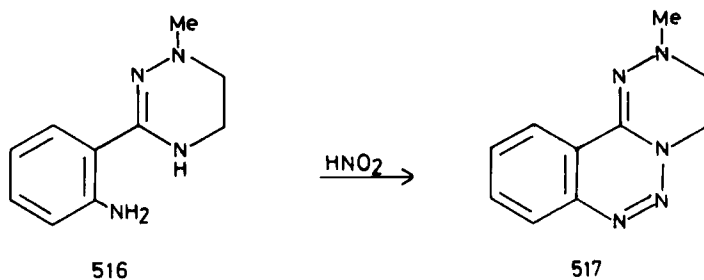
B. [1,2,4]TRIAZINO[*x,y-z*][1,2,4]TRIAZINES

1. [1,2,4]Triazino[4,3-b][1,2,4]triazines

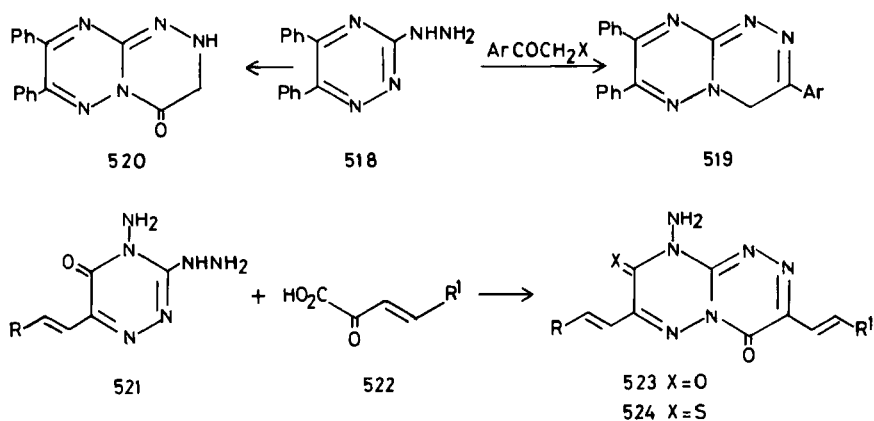
The synthesis of the triazinotriazines **519** was achieved (87M15) by reaction of 3-hydrazino-5,6-diphenyl[1,2,4]triazine **518** with 4-substituted phenacyl halides. These triazinotriazines were screened against P-388 lymphocytic leukemia in mice and were inactive.

Reaction of **518** with various bifunctional compounds such as α -halogeno acids or esters results in the isolation of fused heterocyclic systems such as **520** [87IJC(B)110]. The factors affecting cyclization are dependent on the cyclizing agent as well as the nature of the side chain present in the parent compound.

Arylidenepyruvic acids **522** on reaction with 3-hydrazino[1,2,4]triazine derivative **521** gave the triazinotriazine **523** (90MI2). The thioxo analogue **524** was obtained by the action of Lawesson's reagent on **523**.



SCHEME 120

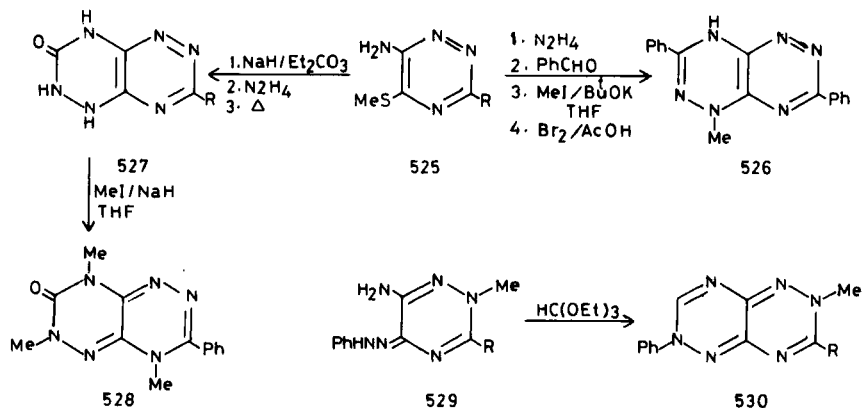


SCHEME 121

2. [1,2,4]Triazino[6,5-e][1,2,4]triazines

The triazines **525** were converted (83TL1767) to the triazinotriazine derivative **526** and **527** by four and three steps, respectively. Methylation of **527** gave **528**.

Derivatives of **530** have been prepared (88S877) from the triazine **529**, which is obtained from the corresponding 5-thiotriazines.



SCHEME 122

C. [1,3,5]TRIAZINO[*x,y-z*][1,2,4]TRIAZINES1. [1,3,5]Triazino[1,2-*b*][1,2,4]triazines

This ring system is represented by tricyclic ring system **533** (76JHC1249). Reaction of 3-hydrazino[1,2,4]triazin-5-ones **531** with 3-iminobutyronitrile afforded 6-methyl- (or phenyl-) 3-[3-methyl-5-aminopyrazolyl]-2,5-dihydro[1,2,4]triazin-5-ones **532A**, which may exist in tautomeric form **532B**. Its reaction with diethoxymethyl acetate (DEMA) or *ortho*-esters afforded the tricyclic compounds **533**.

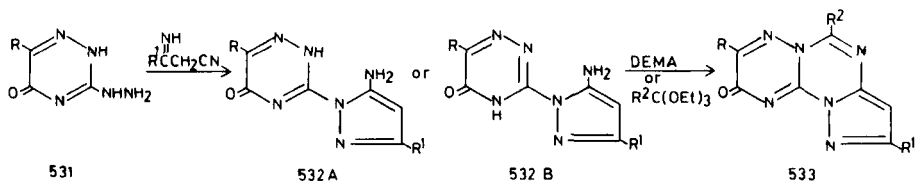
2. [1,3,5]Triazino[2,1-*c*][1,2,4]triazines

Treatment of the triazine derivative **534** with ethylene chlorohydrin gave **535**, whose thermolysis gave (81KGS1125) the triazinotriazine derivative **536**.

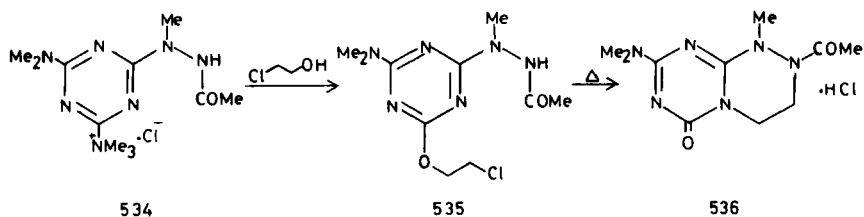
The ring system in **541** was synthesized (76JHC1249) by interaction of 4-hydrazino-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine **540** and ethyl pyruvate. The hydrazino derivative **540** was prepared on cyclocondensation of 5-amino-1-thioamido-3-phenylpyrazole **537** with triethyl *ortho*-formate to give the pyrazolotriazinethione **538** followed by methylation to give **539** and hydrazinolysis to give **540**.

3. [1,3,5]Triazino[2,1-*f*][1,2,4]triazines

[1,3,5]Triazino[2,1-*f*][1,2,4]triazines **543** were prepared [85LA(4)57] by reaction of 6-amino-5-(methylthio)-1,2,4-triazines with the dimer **542**.



SCHEME 123



SCHEME 124

VIII. Triazino-oxadiazines

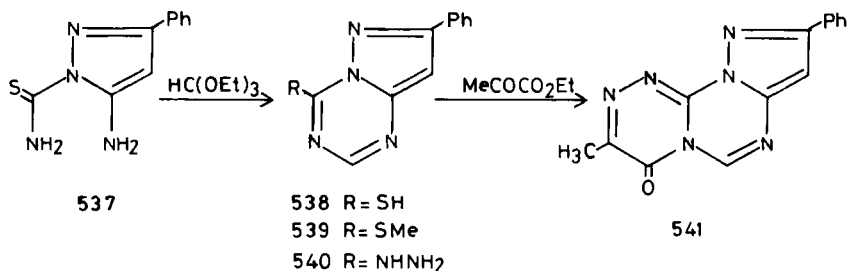
A. [1,2,4]TRIAZINO[x,y-z]OXADIAZINES

1. [1,2,4]Triazino[4,3-d][1,3,4]oxadiazines

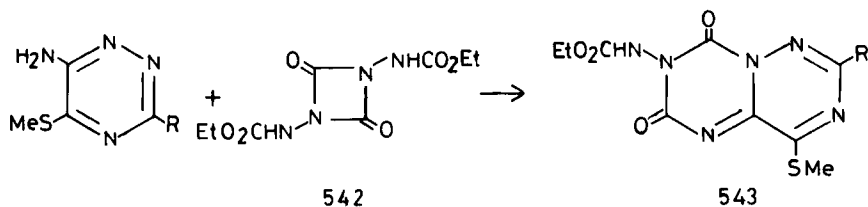
Cyclocondensation of oxadiazinethione derivative **544** with hydrazines gave **545**. Thione **544** was prepared by N-alkylation of the respective oxadiazinone, followed by conversion to the thione (91JIC574).

2. [1,2,4]Triazino[5,6-e][1,3,4]oxadiazines

[1,2,4]Triazino[5,6-e][1,3,4]oxadiazine derivatives **548** were synthesized through the reaction of phenylhydrazine with diethyl oxalate and acid chlorides to give **546**, which then reacted with amidrazone to give triazinones **547**, and then cyclized with thionyl chloride to give the triazino-oxadiazinium chlorides **548** (87S128).



SCHEME 125



SCHEME 126

IX. Triazino-thiadiazines

A. [1,2,4]TRIAZINO[*x,y-z*]THIADIAZINES

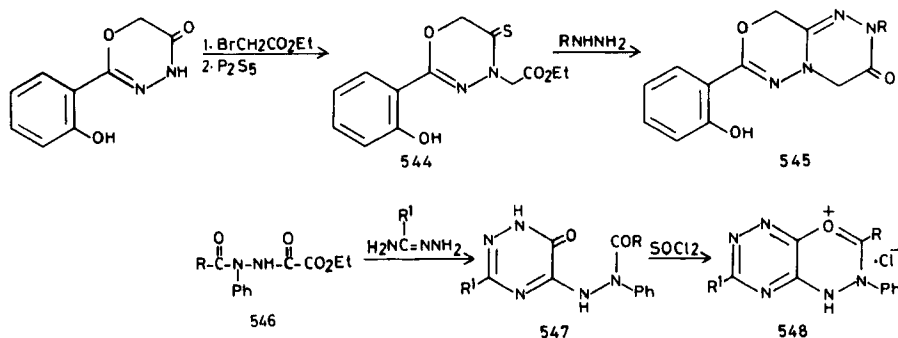
1. [1,2,4]Triazino[3,4-*b*][1,3,4]thiadiazines

The triazinothiadiazines **550** were prepared by cyclocondensation of 4-amino-3-mercapto-6-methyl[1,2,4]triazin-5(4*H*)-one (**549**) with phenacyl halides. These compounds possess fungicidal activity, but none possess bactericidal activity [78IJC(B)481]. Derivatives belonging to this ring system were used as light-sensitive photographic recording materials (82EUP45427).

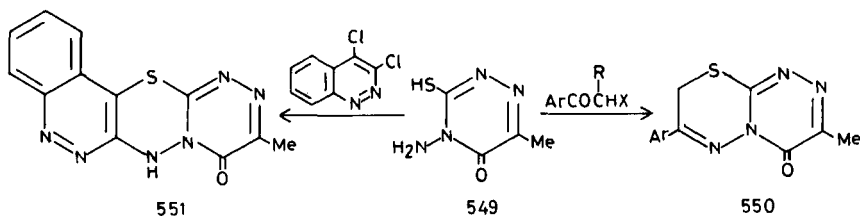
The [1,2,4]triazino[3',4':2,3][1,3,4]thiadiazino[5,6-*c*]cinnolin-9-one **551** was prepared (90JIC351) by cyclocondensation of 3,4-dichlorocinnoline with the triazine derivative.

2. [1,2,4]Triazino[5,6-*e*][1,3,4]thiadiazines

The [(thioacyl)hydrazino]triazines **554** were synthesized from 6-amino-5-hydrazino[1,2,4]triazines **552** by reaction with **553**. Cyclization of **554** with an aqueous mineral acid gave (88S778) the triazinothiadiazine **555**.



SCHEME 127



SCHEME 128

X. Triazino-dioxazines

A. [1,2,4]TRIAZINO[6,1-*d*][1,3,5]DIOXAZINES

The photochemical reaction of azathymine derivative **556** with acetone afforded **557** (89MI2). The proposed reaction mechanism involved a biradical intermediate, which was trapped with a second mole of acetone.

XI. Triazino-oxathiazines

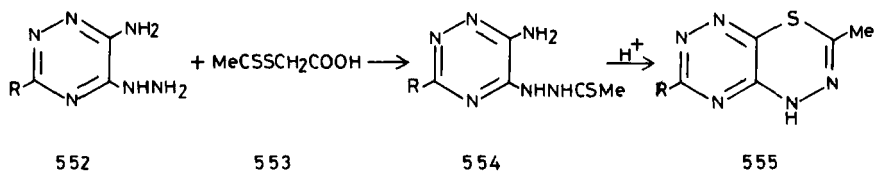
A. [1,2,4]TRIAZINO[6,5-*e*][1,2,3]OXATHIAZINES

The triazino-oxathiazines **559** were prepared by cyclocondensation of phenylhydrazone derivatives **558** with chlorosulfonyl isocyanate. The formation of **559** was dependent on the substituents (91SC1695).

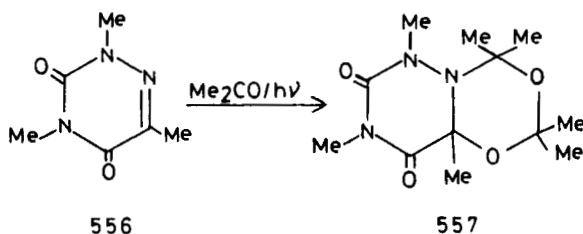
XII. Triazino-tetrazines

A. [1,2,4]TRIAZINO[4,3-*b*][1,2,4,5]TETRAZINES

The iminophosphorane **560** reacts with acyl chlorides in the presence of triethylamine in benzene at a reflux to give (88T2249) the corresponding [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines **563**. When the reaction was carried



SCHEME 129



SCHEME 130

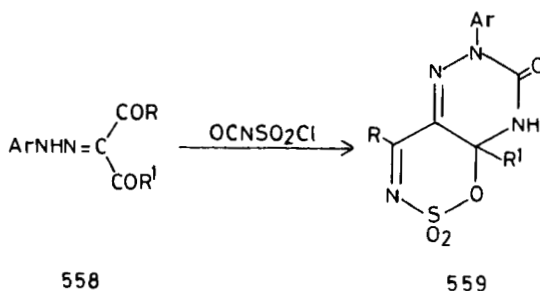
out at room temperature, acyl derivatives **561** were obtained. Subsequent reaction with isocyanates gave **563** via **562** [89JCS(P1)247]. Condensation of **560** with carbonyl compounds gave tetrahydrotriazinotriazines **564**. Dehydrogenation of **564** gave **565**.

XIII. Triazino-azepines

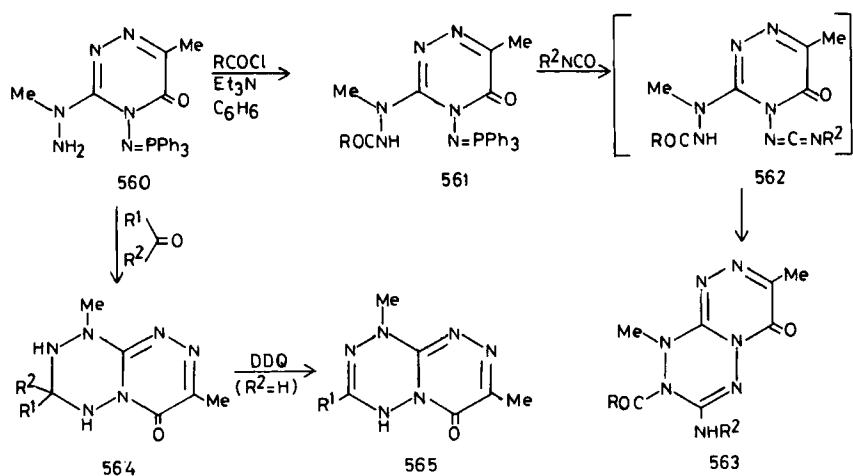
Few examples are reported for triazino[x,y-z]azepine ring systems.

A. [1,2,4]TRIAZINO[4,3-*a*]AZEPINES

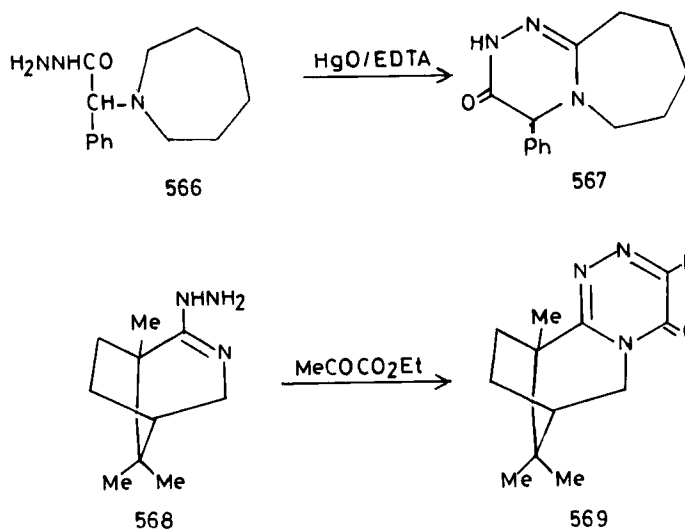
Dehydrogenation of **566** gave **567** (77AP588). Ring closure of the hydrazine **568** with ethyl pyruvate gave methanoazepinotriazine **569** (86H907).



SCHEME 131



SCHEME 132



SCHEME 133

XIV. Triazino-diazepines

A. [1,2,4]TRIAZINO[*x,y-z*][1,4]DIAZEPINES

1. [1,2,4]Triazino[4,3-*a*][1,4]diazepines

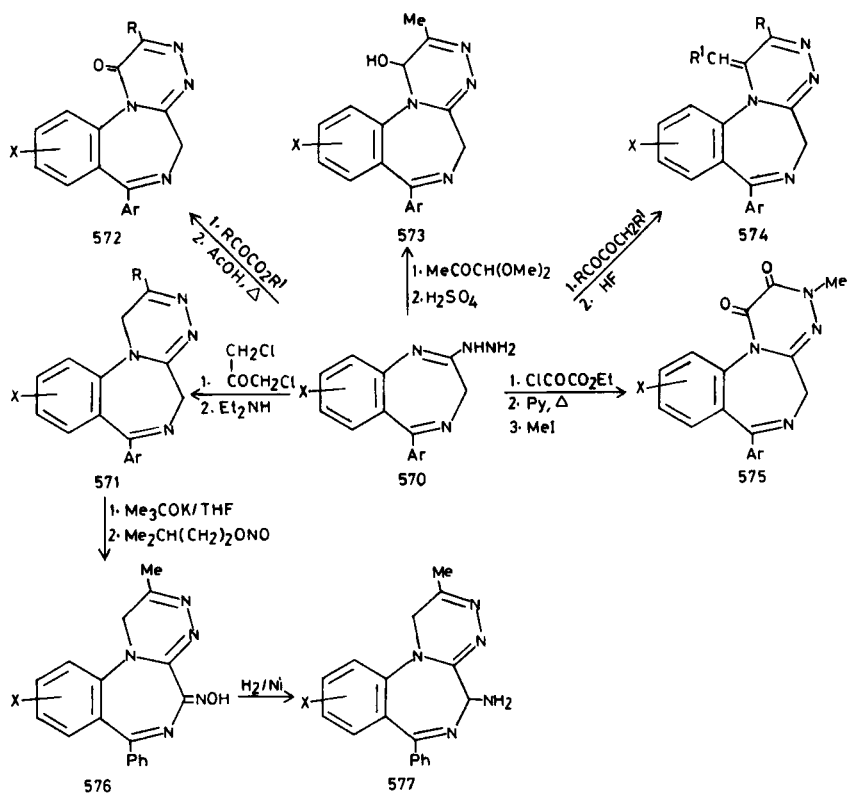
A series of [1,2,4]triazino[4,3-*a*][1,4]benzodiazepines **571**–**575** were prepared, which differed in the degree of unsaturation and the position of oxygen in the triazino ring (77JHC1231). These were prepared by closing the triazino ring of appropriately substituted hydrazones from 2-hydrazinobenzodiazepines **570** or by condensing substituted hydrazines with 2-thiobenzodiazepines. Most of these represent new ring systems (77USP4016165). Compounds **572** ($R = \text{CH}_3$) (77USP4017492) was brominated, then treated with Et_2NH to give **572** ($R = \text{CH}_2\text{NEt}_2$). Its analogue **571** was also obtained by reaction of **570** with 1,3-dichloropropanone followed by reaction with dimethylamine (77USP4028356). Compounds having this ring system were reported to be tranquilizers, muscle relaxants, and anticonvulsants, and to have central nervous system activity indicating anxiolytic, hypnotic or sedative potential (77USP4017492; 78USP4073784, 78USP4073785, 78USP4086230).

The reaction of **571** with isopentyl nitrite in the presence of potassium tert-butoxide gave 5-oximinotriazinobenzodiazepine **576**, which was hydrogenated over Raney nickel to give aminotriazinobenzodiazepine **577** (88EUP272868).

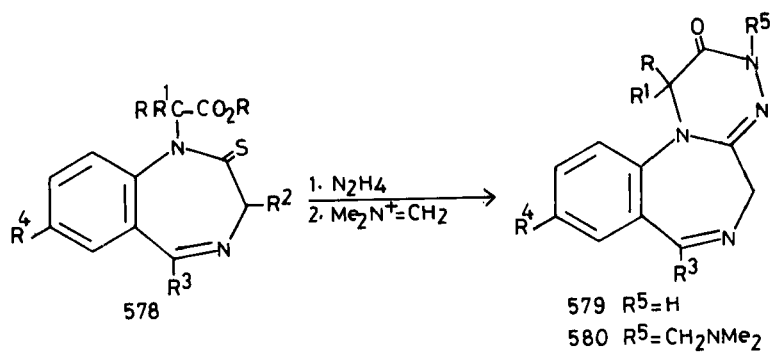
Triazinobenzodiazepines **579** were prepared (75USP3882112; 76USP3933816) by cyclization of **578** with hydrazine. Precursors **578** were prepared by treating benzodiazepines with α -bromoesters followed by phosphorus pentasulfide. Treatment of **579** with $\text{Me}_2\text{N}^+ = \text{CH}_2\text{Cl}^-$ gave **580**. These compounds were reported to be tranquilizer and antianxiety agents as well as sedative and muscle relaxants (76USP3933816; 77USP4017492).

2. [1,2,4]Triazino[5,6-*b*][1,4]diazepines

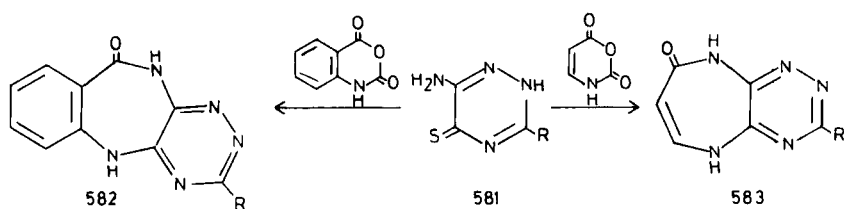
The first representative of the [1,2,4]triazino[5,6-*b*]diazepin-8-ones **583** was obtained by reaction of 6-amino-3-(*p*-tolyl)[1,2,4]triazin-5(2*H*)-thione **581** with 2*H*-1,3-oxazine-2,6(3*H*)-dione [85LA(3)640]. The benzo analogue [1,2,4]triazino[5,6-*b*][1,4]benzodiazepinones **582** were similarly obtained by reaction of **581** with isatoic anhydride.



SCHEME 134



SCHEME 135



SCHEME 136

3. [1,2,4]Triazino[4,3-d][1,4]diazepines

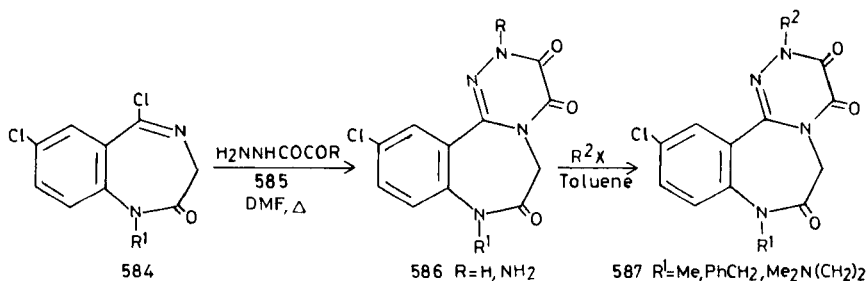
Cyclocondensation of chloroimide **584** with **585** ($R = \text{morpholino}$) in DMF gave **586** ($R = H$) probably via the formation of the amidrazone as an intermediate (75GEP2447467, 75USP3898212; 77TL1699). On the other hand, the reaction of **584** with **585** ($R = \text{NH}_2$) gave **586** ($R = \text{NH}_2$) as a minor product in addition to the triazolo[4,3-*d*][1,4]benzodiazepin-6-one (77TL1699). Alkylation of the salt of **586** with alkyl halide in toluene gave **587**, useful as antiphlogistics or nervous system depressants and anti-inflammatory agents (75GEP2447467).

XV. Triazino-triazepines

A. [1,2,4]TRIAZINO[*x,y-z*]TRIAZEPINES

1. [1,2,4]Triazino[4,3-b][1,2,4]triazepines

Condensation of **588** with ethyl acetoacetate gave **589a**, in poor yield together with isomeric **589b** and 2-methyl-7-oxo-3,7-dihydro-



SCHEME 137

1,2,4-triazolo[3,2-*c*][1,2,4]triazine (75JHC1095). The mass spectra of triazinotriazepinones have been reported (760MS680).

2. [1,2,4]Triazino[4,3-*d*][1,2,4]triazepines

Cyclization of the hydrazinotriazepine derivative **590** with phenacyl bromide in methanol at 20°C afforded the triazinotriazepine **591**. The same reactants at reflux for 2 h gave a pyridazinotriazepine derivative [78JCR(S)190].

XVI. Heterocyclo-triazino Heterocycles

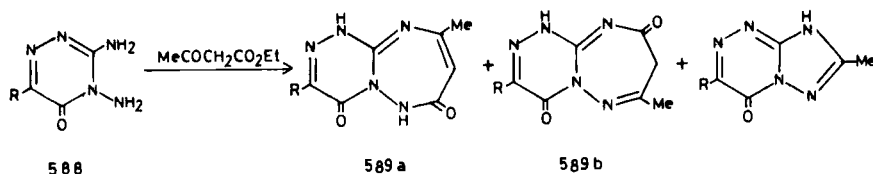
A. HETEROCYCLO-TRIAZINO-INDOLES

1. Imidazo-triazino-indoles

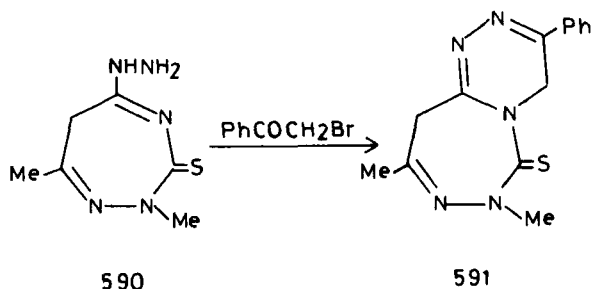
Condensation of **592** with phenacyl halides gave the imidazotriazino-indoles **594**. However, the reaction with formamidine derivative **593** afforded isomeric derivative **595** (87MI5).

The imidazo[1,2-*b*][1,2,4]triazino[5,6-*b*]indoles **597** were prepared by reacting 3-amino[1,2,4]triazino[5,6-*b*]indole **592** with α -bromoketones **596**. The structure was confirmed by the identity with the product of a reaction between isatin **599** or 2-phenylimino-3-oxoindole **600** and 1,2-diamino-4,5-diphenylimidazole **598** (82ZOR1272). Similarly, a cyclocondensation of 1,2-diamino-4-arylimidazoles with isatin and N-methylisatin was carried out (82KGS242).

Compounds **594** were screened against P-388 lymphocytic leukemia in mice and were inactive.



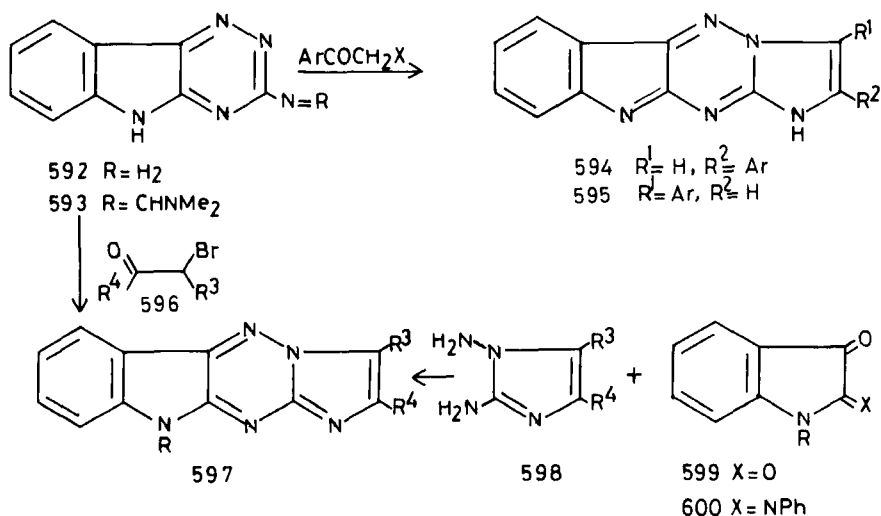
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2. Thiazolo-triazino-indoles

Condensation of **601** with phenacyl halides gave **602**, which cyclized to furnish thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indoles **604** and not the angular isomeric **606** [76IJC(B)541; 81JPR159; 91IJC(B)1098]. The structure of **604** was confirmed by unequivocal synthesis of the angular isomer **606**, which has been accomplished by the reaction of 2-hydrazino-4-arylthiazoles **608** with isatin to give **607**, followed by cyclization with polyphosphoric acid. On the other hand, cyclocondensation of isatin thiosemicarbazones with monochloroacetone gave isatin thiazolyhydrazones, which underwent intramolecular condensation to give the respective linear



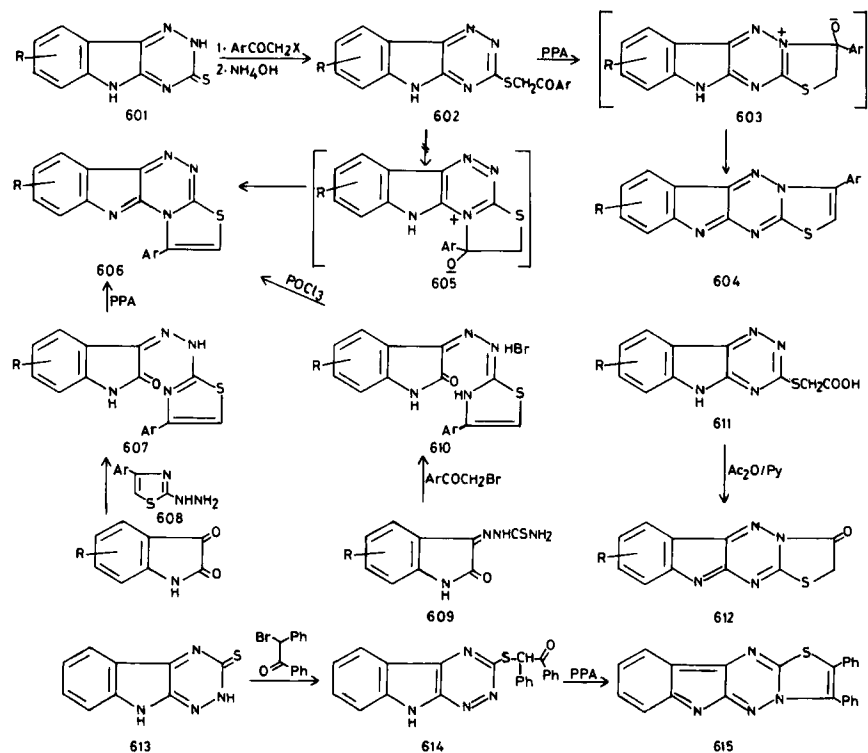
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and angular thiazolotriazinoindoles (90MI4). The reaction of **609** with phenacyl halides gave **610**, which cyclized by phosphorus oxychloride to give **606** [82IJC(B)311, 82MI1]. The mode of the cyclization of **602** to give **604** was suggested to be due to the greater stability of cyclic transition state of **603** than of **605**, a consequence of the absence of steric repulsion due to crowding between the NH of the indole ring and the aryl group [76IJC(B)541]. The intermediate **603** underwent a prototropic change followed by loss of a water molecule to give **604**. The antibacterial and antifungal activities have been evaluated [87IJC(B)535; 89JIC252].

Treatment of **601** with chloroacetic acid, followed by cyclodehydration of **611** afforded **612** [76IJC(B)541].

Condensation of **613** with α -bromo- α -phenylacetophenone gave **614**, whose cyclization was effected by polyphosphoric acid to give **615** (82ZOR1272).

Condensation of **601** with 1,2-dibromoethane and 1,3-dibromopropane

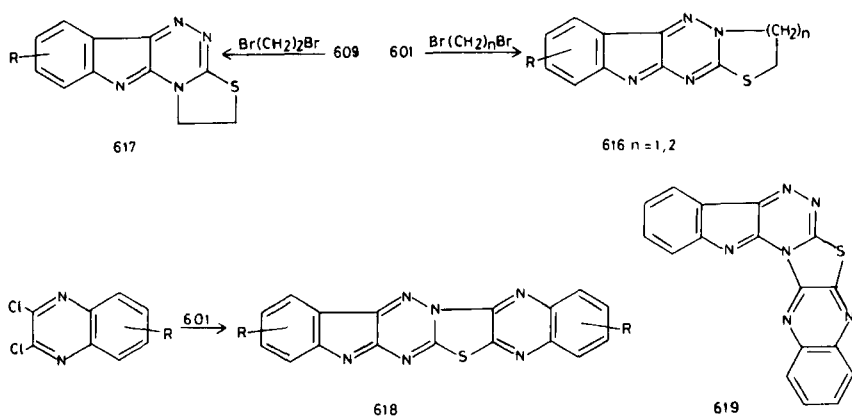


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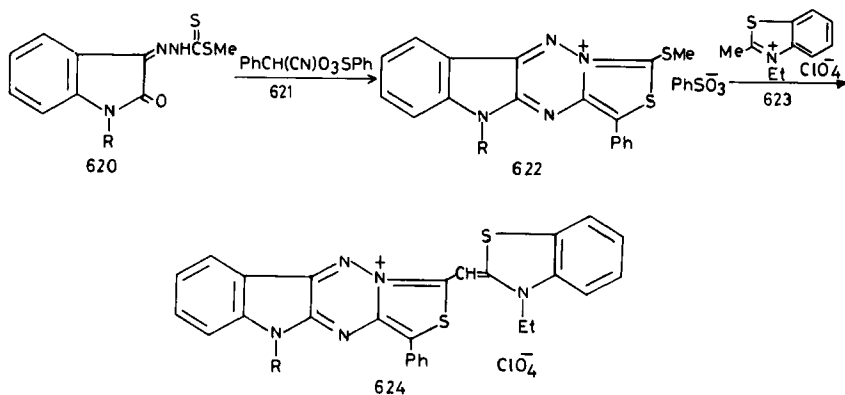
gave products whose structures were reported to be isomers thiazolo- and thiazino[3',2':2,3][1,2,4]triazino[5,6-*b*]indoles **616** or the angular isomers **617** [76IJC(B)541; 82IJC(B)311, 82MI1, 88IJC(B)731; 90IJC(B)438, 90IJC(B)645; 91IJC(B)1098]. Moreover, it was suggested that the intermediate leading to **617** is devoid of steric repulsions, shown before for the phenacyl derivatives, and consequently is stable enough to undergo prototropic changes to give the angular isomer (91IJC(B)1098). Angular isomer **617** [87IJC(B)535; 90IJC(B)645] could be unequivocally synthesized by the cyclization of isatin-3-thiosemicarbazones **609** with 1,2-dibromoethane. These compounds were tested for bactericidal and fungicidal activity and for antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* [90IJC(B)645, 90IJC438].

Indolo[2'',3':5',6'] [1,2,4]triazino[3',2':2,3]thiazolo[4,5-*b*]quinoxaline **618** was prepared by condensation of **601** with 2,3-dichloroquinoxaline [76IJC(B)541; 88IJC(B)346; 90IJC(B)645, 90IJC438]. However, the angular product **619** was suggested for one of the derivatives [88IJC(B)731; 92MI3].

Cyclocondensation of isatin hydrazones **620** with **621** in strong acid gave thiazolo[3',4':2,3][1,2,4]triazino[5,6-*b*]indoles **622**, which underwent conventional reaction with 2-methyl-3-ethylbenzothiazolium perchlorate **623** to form unsymmetrical cyanines **624** (83URP1054350; 85KGS211). The spectral properties of a series of polymethine dyes were examined (88KGS1547).



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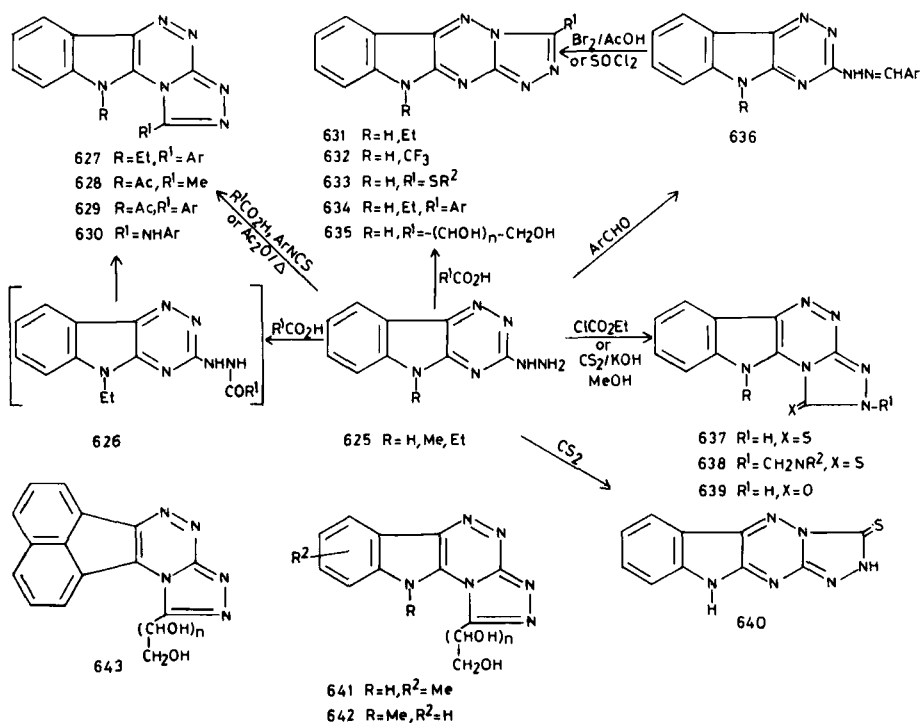
SCHEME 143

3. Triazolo-triazino-indoles

Cyclization of the hydrazino group at the 3-position of the triazino-indole ring system with one carbon inserting reagents has proven to be a valuable method for the synthesis of triazolo-triazino-indoles, which are significant pharmacologically. However, there is a considerable controversy about the structure of the products: linear or angular. Thus, condensation of 3-hydrazino-5H-1,2,4-triazino[5,6-*b*]indole **625** (R = H) with organic acids gave 3-substituted[1,2,4]triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indoles **631** (82ZOR1272; 87JHC1435), whereas the 5-ethyl analogue **625** (R = Et) or the parent unsubstituted analogue gave with organic acids 10-ethyl-10H-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indoles **627** (87AP1191, 87AP1196, 87MI4). The reaction proceeded through N-2 acylation of the hydrazino group to give **626**, followed by thermal cyclization at N-2 or N-4 of the triazine ring (87AP1191). The mass spectral fragmentation of **627** has been studied (90MI1). Treatment of **625** (R = H) with boiling acetic anhydride was reported (89JHC769) to give 10-acetyl-1-methyl-10H-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **628**, whereas the linear isomer **632** was reported (81H43) to be the product from the reaction of **625** (R = H) with trifluoroacetic anhydride in acetic acid. Cyclization of **625** with carbon disulfide in methanol led to the synthesis of [1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **637** (87AP1196; 89JHC769, 89JIC690; 91H1081), whereas structure **640** was reported in earlier reports (87JHC1435) and its alkylation product was reported as **633** (87JHC1435). Mannich reaction of **637** with formaldehyde and secondary amines afforded the Mannich bases **638** (91H1081). These compounds showed anti-

viral activity but no antibacterial activity. Cyclization of **625** (87AP1191; 89JHC769) with ethyl chloroformate yielded **639**. Reaction of **625** ($R = H$) with aromatic aldehydes gave the corresponding hydrazones **636** ($R = H$) that cyclized with bromine in acetic acid to give **634** ($R = H$) (87JHC1435). Ring closure of **636** was also affected by the use of thionyl chloride (90JIC79). Also, the hydrazones **636** ($R = Et$), obtained from the reaction of **625** ($R = Et$) with aromatic aldehydes, were cyclized with thionyl chloride to give **627** ($R = Et$) (87AP1196). Reaction of **625** ($R = H$) with *p*-nitrobenzaldehyde or 1-naphthaldehyde in presence of acetic acid was reported (89JHC769) to give the angular triazolo-triazinoindoles **629**. Cyclocondensation of **625** with arylisothiocyanates gave **630** (86MI3). The structure-activity relationship of some of these compounds was discussed (84AAC195; 87KPS155).

The cyclization of sugar hydrazones of **625** by the action of iron(III) chloride gave **635** or **642**, depending on the substituent on the indole ring (92BCJ546; 93SL1817; 94JPRip). The presence of a methyl group on the



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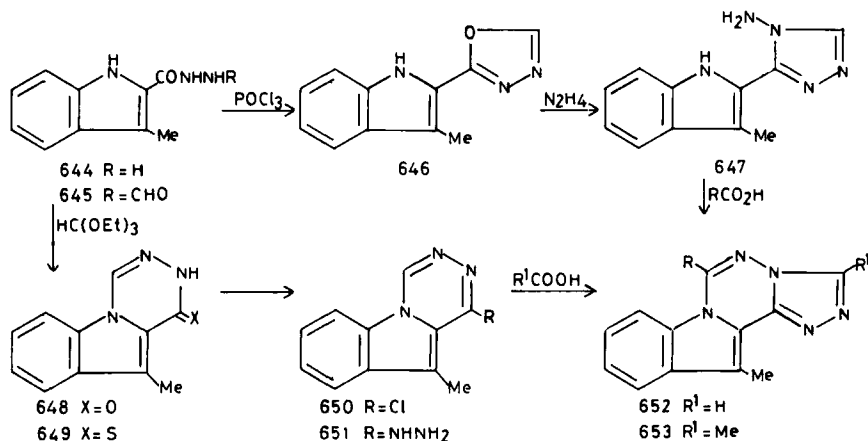
benzene ring also directed the cyclization to give **641** (94UP1). Similarly, **643** was prepared (93BCJip).

Formylation of indole-2-carbohydrazides **644** gave the formylindole-2-carbohydrazide **645**, which cyclized with phosphorus oxychloride to the corresponding 1,3,4-oxadiazolylindole **646**. Treatment of the latter with hydrazine, followed by cyclization with formic or acetic acid gave [1,2,4]triazolo[3',4'-f][1,2,4]triazino[4,5-a]indoles **652** and **653**, respectively [90IJC(B)372].

Treating **644** with triethyl orthoformate gave 1,2-dihydro-1-oxo[1,2,4]-triazino[4,5-a]indole **648**, whose reaction with phosphorus oxychloride or phosphorus pentasulfide gave **650** and **649**, respectively. Both reacted with hydrazine to give **651**, which then was converted into [1,2,4]triazolo[3',4'-f][1,2,4]triazino[4,5-a]indoles **652** and **653** by reaction with formic or acetic acid, respectively (80JHC77).

4. Tetrazolo-triazino-indoles

The reaction of **625** ($R = H$) with nitrous acid (sodium nitrite/phosphoric acid) was reported (89JHC769) to give the azido derivative **654** instead of the previously reported tetrazolo analogue **656** ($R = H$) (80JHC1783). The cyclization of the azide was affected by acetic anhydride to give the angular tetrazole **656** ($R = Ac$) with simultaneous acetylation (89JHC769). The formation of the angular structure is favored in comparison to linear **655** because the 10π -electron system of the indole ring is preserved in the former. However, linear structure **655** was reported to be the product



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(80AP108) from the reaction of hydrazine with sodium nitrite in acetic acid. Treatment of **625** ($R = Et$) with sodium nitrite in acetic acid gave **656** ($R = Et$) through the 3-azido valence tautomer **654** ($R = Et$) (87AP1191).

5. *Pyrimido-triazino-indoles*

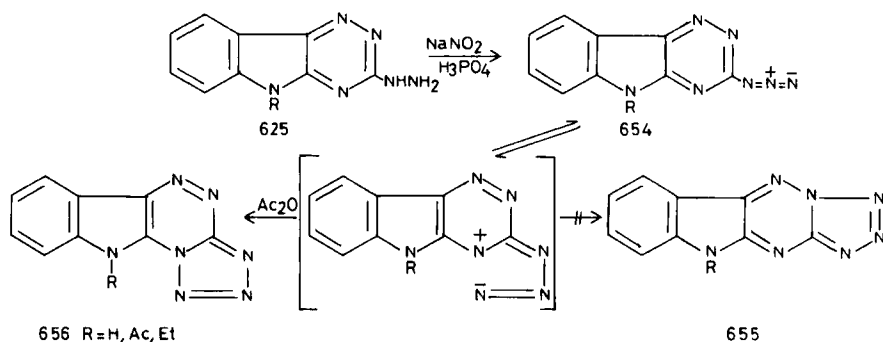
Heating an intimate mixture of bis(2,4,6-trichlorophenyl)malonate and the appropriate 3-aminotriazinoindoles **657** afforded pyrimido-[3',2':2,3][1,2,4]triazino[5,6-*b*]indole-2,4-diones **658** (88JHC475).

6. *Quinazolino-triazino-indoles*

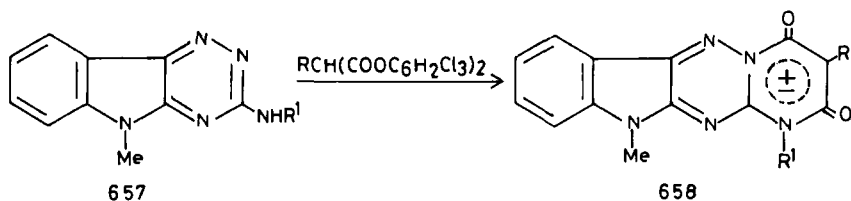
Reaction of isatin derivatives with 2,3-diaminoquinazoline in ethanolic KOH gave indolotriazinoquinazolinones **359** and triazinoquinazolinedi-ones **360**, probably through a Schiff base intermediate. Such compounds showed a significant antibacterial activity [92IJC(B)105].

7. *Triazepino-triazino-indoles*

3-Hydrazino-5*H*-[1,2,4]triazino[5,6-*b*]indoles **625** were condensed with ethyl acetoacetate in absolute ethanol to give **661** ($R^1 = Et$) (89JHC545). On the other hand, 3-(5'-hydroxy-3'-methyl-1*H*-pyrazol-1-yl)-5*H*[1,2,4]triazino[5,6-*b*]indole was reported (89JHC769) to be the product from a similar reaction. Compound **661** ($R = Et$) on alkaline hydrolysis afforded the corresponding acid, which on heating with acetic acid yielded a variety of products depending on the substituents on the indole ring. Cyclization of **661** ($R^1 = H$) furnished two products in a 3:1 ratio. The major compound was identified to be 3-methyl-1-oxo-12*H*-1,2,4-triazepino-



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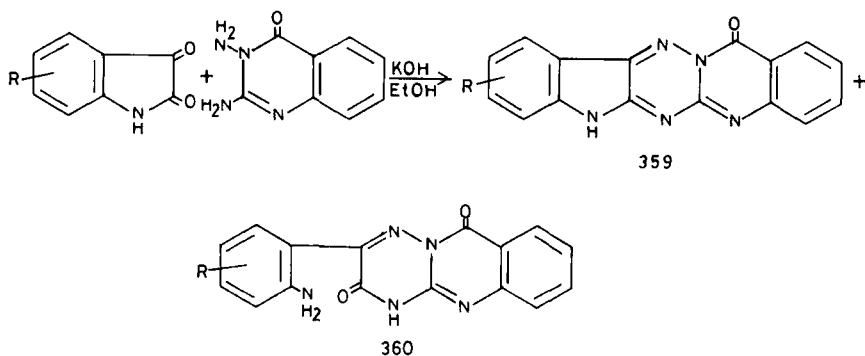
SCHEME 147

[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **662** (R=H) with cyclization at N-4, whereas the minor product was identified as 3-methyl-5-oxo-12*H*-1,2,4-triazepino[4',3':2,3][1,2,4]triazino[5,6-*b*]indole **663**. Compound **661** (R=Me) afforded a single product **662** (R=Me). Cyclization at N-4 is presumed to be favored in view of the stability of the benzenoid structure and the product has been tentatively assigned the angular structure (89JHC545).

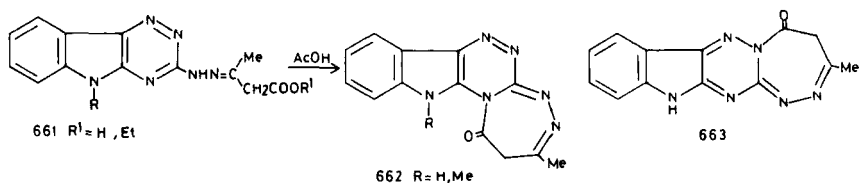
B. MISCELLANEOUS

Furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazines **667** were prepared by reaction of **664** with phosphorus pentasulfide to give **665** followed by conversion to the hydrazino derivative **666** and subsequent cyclization with *ortho*-esters (84CCC65, 84MI3). Similarly, the indolo analogue **670** was prepared from **668** by sulfurization and hydrazinolysis to give **669**, which cyclized with *ortho*-esters (84CCC1529).

The reaction of 4-methyl-2,3,4,6-tetrahydro[1,2,4]triazino[3,4-*a*]-isoindole-3,6-dione **671** with 3-dimethylamino-2,2-dimethyl-2*H*-azirine



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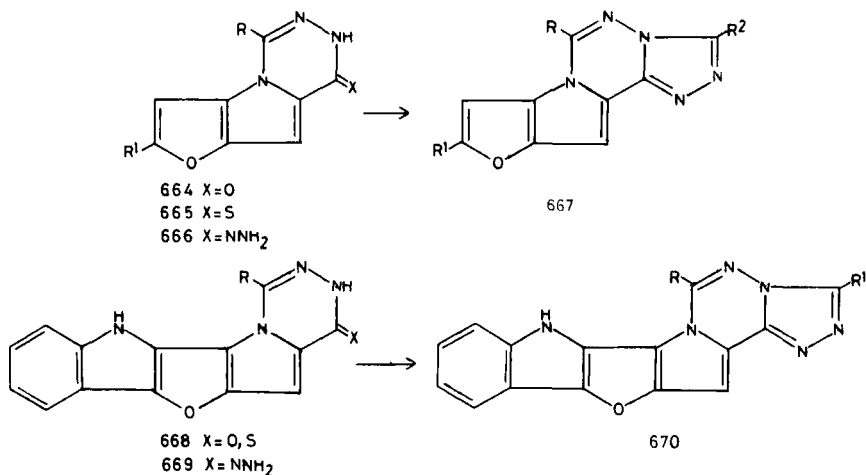
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672 gave 2,2,4-trimethyl-2,4-dihydro-1*H*,6*H*-imidazo[1',2':1,6][1,2,4]-triazino[3,4-*a*]isoindol-1,6-dione **673**, whose structure was confirmed by X-ray analysis (80HCA1797).

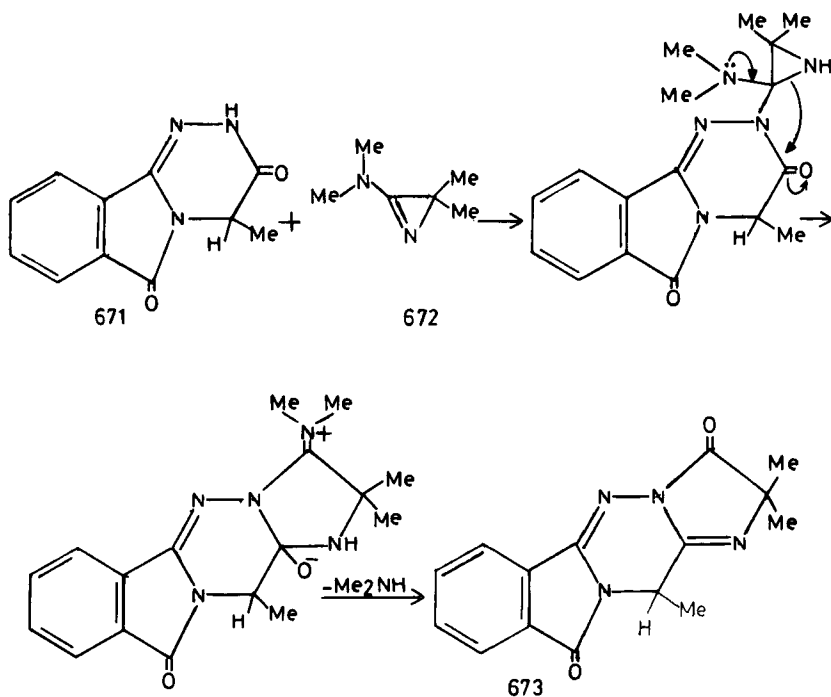
1-Phenylpyrazolo[3,4-*e*]pyrrolo[2,1-*c*][1,2,4]triazine **675** was prepared (84H2513) from 4-amino-1-phenyl-5-(pyrrol-1-yl)pyrazole **674** with sodium nitrite in an acidic medium.

Cyclization of phenacyl derivatives **676** and **678** with phosphorus oxychloride and pentachloride gave **677** and **679**, respectively (87KGS533).

To expand the range of model conformations of cyclonucleosides, synthesis of some long-bridged purine cyclonucleosides [78CC86; 81JOC-5176; 85JCS(P1)2347] has been achieved. Thus, heating 8-bromo-2'-*O*-tosyladenosine **680a** and its guanine **680b** or hypoxanthine **680c** analogues with excess methylhydrazine or hydrazine in methanol gave the corresponding cyclonucleosides **681**, which on treatment with nitrous acid in acetic acid yielded cycloinosine **682a** and its xanthine analogue **682b**,



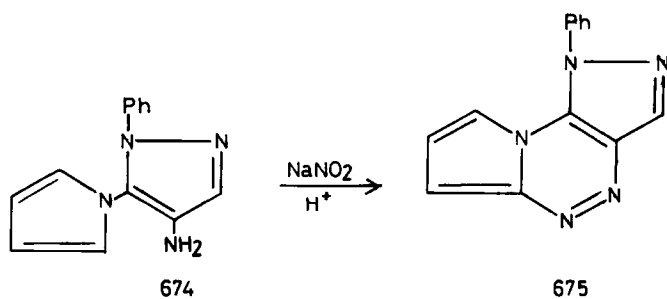
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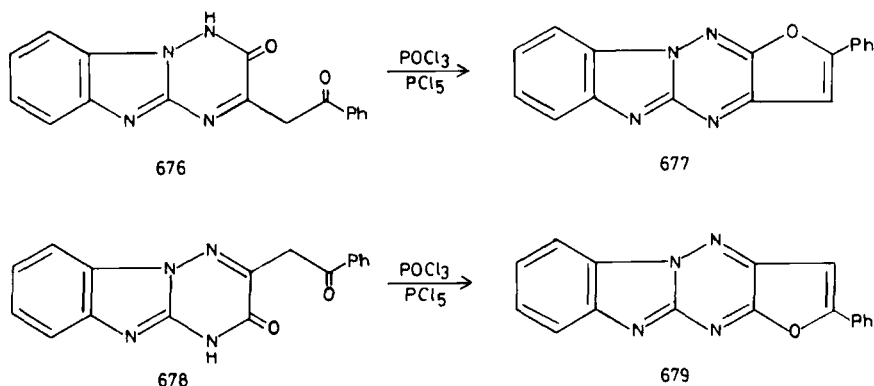
SCHEME 151

respectively. Oxidation of **681a** with NaIO_4 or MCPBA gave the analogue cycloadenosine **682c**. Acetylation of **682** gave **683** (81JOC5176), which on reduction with NaBH_4 gave **684**. The reactions could be also carried out using hydrazine.

Oxidation of **681a**, **681c** with hypobromous acid generated *in situ* [85JCS(P1)2347] gave the corresponding cyclonucleosides **682c**, **682a**,



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SCHEME 153

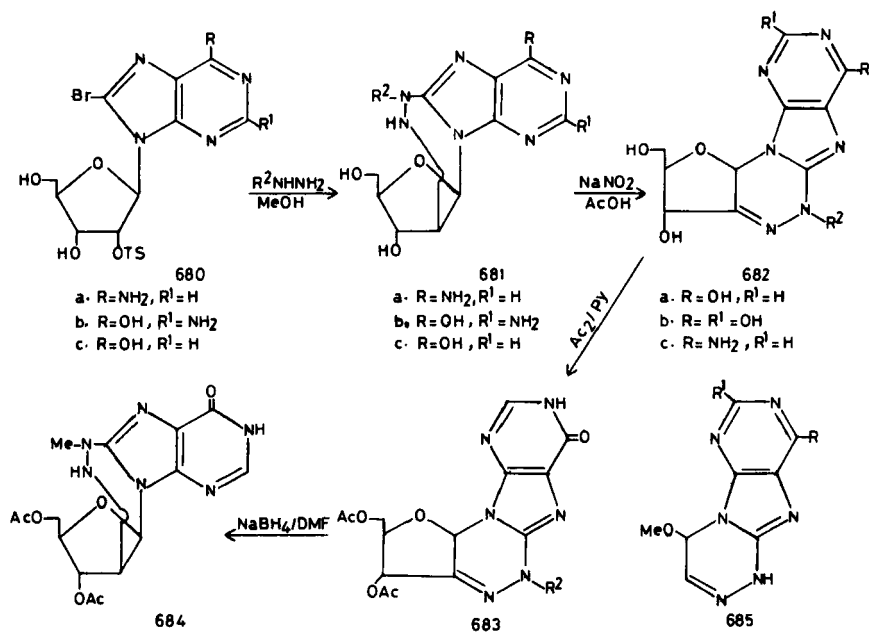
whereas similar oxidation of **681b** was abandoned owing to its very limited solubility in most organic solvents and water. On the other hand, when **681a** was subjected to sodium methoxide catalyzed aerial oxidation in methanol, it gave the 9-amino-4-methoxy-1*H*-[1,2,4]triazino[3,4-*e*]purine **685** (R=NH₂). Similarly, **681c** gave 9-hydroxy-4-methoxy-1*H*-[1,2,4]-triazino[3,4-*e*]purine **685** (R=OH) on similar oxidation procedure. The reaction may have taken place via **682**. Similarly, the 5'-*O*-trityl analogues were synthesized from **680a** by tritylation and treatment of the formed 8-bromo-2'-*O*-tosyl-5'-*O*-trityl adenosine with an excess of hydrazine to give the trityl analogue of **681**.

The synthesis of some long-bridged purine cyclonucleosides with a diatomic bridge between C₈ and C_{3'} of adenosine as well as inosine by using methylhydrazine as a diatomic bridge component has been reported (82JOC4465). Thus, reaction of 8-bromo-3'-*O*-[(2,4,6-triisopropylphenyl)-sulfonyl] adenosine **686a** and its hypoxanthine analogue **686b** with methylhydrazine gave the corresponding 8-(*N*-methylhydrazino) analogues **687a** and **687b**. Their base-catalyzed cyclization at high temperature gave **688** and **689**, which were converted to 5'-acetyl analogues **690a**. Acidic hydrolysis of **688a** or **690a** gave **691** (82JOC4465).

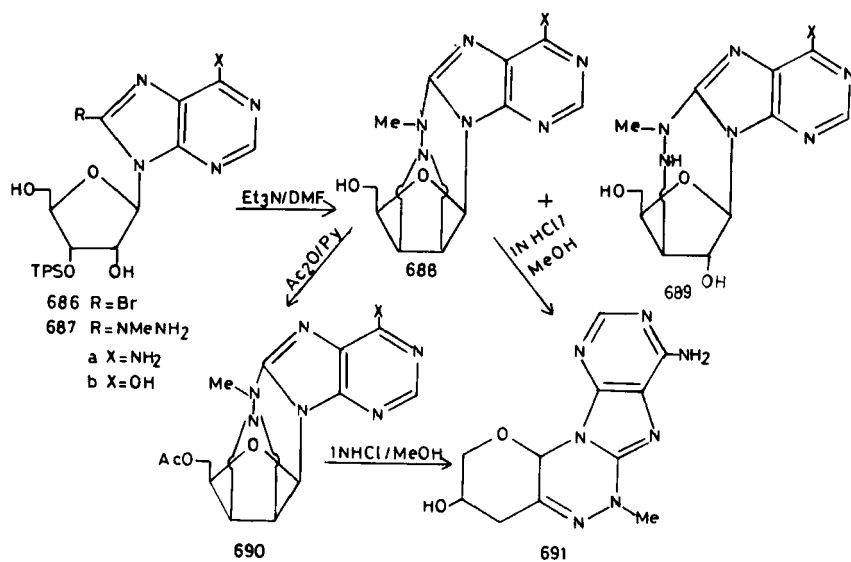
Thieno[2,3-*e*][1,2,4]triazino[4,3-*b*][1,2,4]triazines **693** were prepared by cyclizing **692** with phosphorus pentasulfide (90MI2).

Alkylation of **694** with phenacyl bromides, followed by cyclization with acetic anhydride gave (87H2183) thiazolo[2,3-*c*]pyrido[2,1-*f*][1,2,4]-triazine **695**.

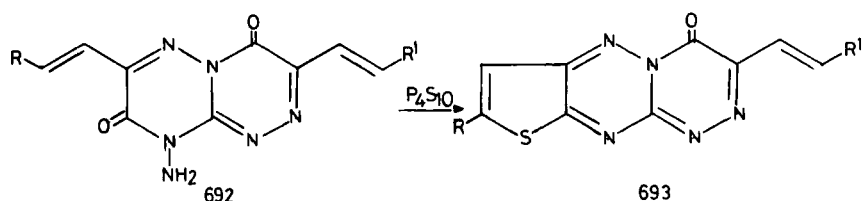
The isoxazolopyrazolotriazines **697** were prepared (88AP141) by treating diazotized aminopyrazoles with *N*-hydroxycyanoacetamide to give **696**, followed by cyclization to give **697**.



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The diazotized 3-amino-4-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile **698** coupled with 1-phenyl-3-methyl-5-pyrazolone **699** to yield **700**, which cyclized (91G209) to the condensed pyrazolotriazine **701**.

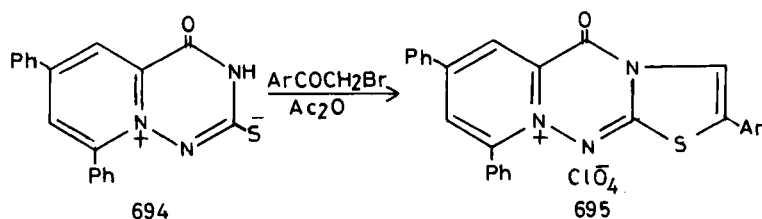
Pyrazolo[3,2-*c*]pyrido[4,3-*e*][1,2,4]triazine oxides **704** were prepared by cyclization of the hydrazone derivatives **703** with ethanolic sodium hydroxide. Subsequent reduction of **704** gave **705** (76JPR835). Hydrazone **703** was prepared by condensation of 4-hydrazino-3-nitropyridine with **702**. The mass spectral fragmentation patterns for **704** and **705** and their benzo analogues were studied (77ZC142).

Alkylation of 2-(pyrazol-1'-yl)pyridine **706** with 1,2-dibromoethane afforded (81JHC9) pyrazolo[1',2'-*a*]pyrido[2,1-*c*][1,2,4]triazinium dibromide **707**.

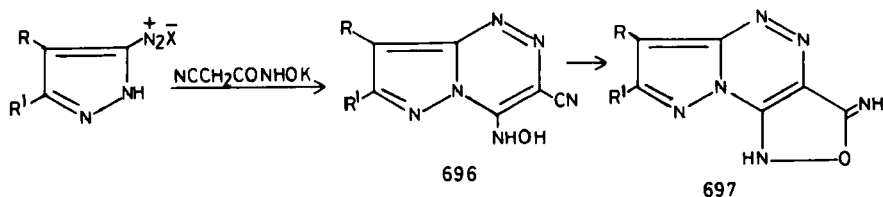
The pyrazolotriazinecarboxylate **708** underwent cyclization with urea or thiourea to give (84PHA432) pyrazolopyrimidinotriazines **711**, and with *o*-phenylenediamine, *p*-chloroaniline, or *o*-aminophenol to give quinolino-pyrazolotriazines **710**. The reaction of the pyrazolo[5,1-*c*][1,2,4]triazine **709** with hydrazine hydrate gave **712**, and its reaction with phenyl isothiocyanate gave **713** (83G219).

Reaction of the betaine **714** with dimethyl acetylene-dicarboxylate gave the cycloadduct **715** (77H281).

Pyrazolo[5',1':3,4][1,2,4]triazino[5,6-*d*]pyrimidine **720** was prepared (89JHC853) by reaction of **716** with formamide. Treatment of **716** with aromatic amines gave **717**, whose cyclization with triethyl *ortho*-



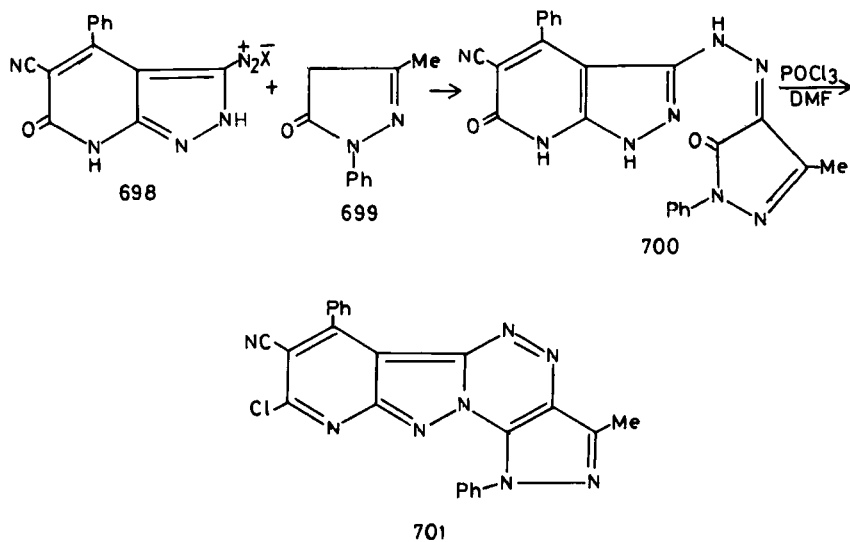
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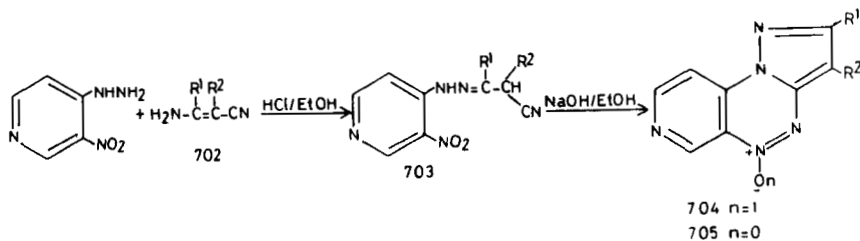
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formate gave **719**. The reaction of **716** as its ethanol complex or the corresponding carboxylic acid ester **718** with a 3-fold molar amount of *o*-phenylenediamine dihydrochloride in acetic acid provided (87JHC1799) 9-ethoxycarbonyl-5*H*,13*H*-2',3'-dihydrospiro[benzimidazole-6,2'-pyrazolo][1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine hydrochloride **723** and 9-ethoxycarbonyl-6-oxo-13*H*-5,6-dihydropyrazolo[1',5':3,4][1,2,4]-triazino[5,6-*b*][1,5]benzodiazepine **722** via the intermediate **721**. Treatment of **723** with 10% sodium hydroxide gave the free base **724**. The reaction of **718**, with a 1.5-fold molar amount of *o*-phenylenediamine hydrochloride in acetic acid also afforded **722** (87JHC1799).

The reaction of **718** with *o*-aminophenol hydrochloride gave (87JHC1805; 88JHC1259) 9-ethoxycarbonyl-6-oxo-5,6-dihydropyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepine **725**, whose alkyla-



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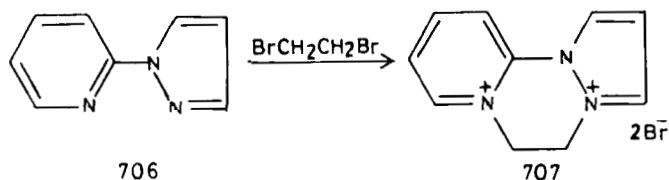


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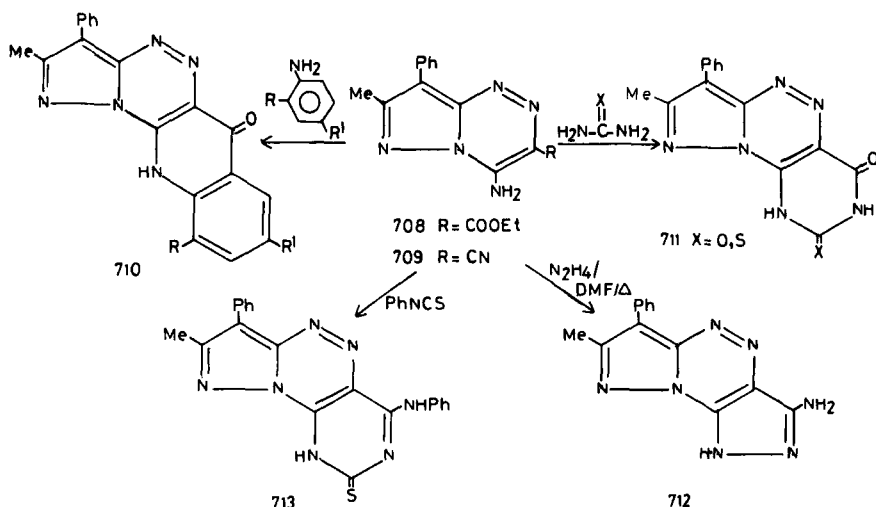
tion with methyl iodide and isopropyl iodide provided **726**. Heating the latter in HCl–HOAc resulted in ring transformation to afford the spiro-[benzoxazole-2'-(3'*H*),4(1*H*)pyrazolo[5,1-*c*][1,2,4]triazines] **727**. Similarly, the reaction of **716** with a three-fold molar amount of *o*-aminophenol hydrochloride produced **729** in addition to **725**. Heating **725** and **729** in HCl–HOAc afforded **728** via the intermediate A. The spiro ring structure was supported by long-range ^{13}C – ^1H COSY and ^{13}C -NMR spectra. Compounds **725**, **726**, and **729** showed a weak antibacterial activity against *Xanthomonas oryzae*, *Rhizoctonia solani* and *Pythium debaryanum*, whereas the spiro compounds **727** and **728** showed no antibacterial and antifungal activities against these microorganisms.

The reaction of **716** or **730** with thiosemicarbazide hydrochloride in acetic acid gave (89JHC861) the pyrazolo[5',1':3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine hydrochloride **732a**, which was treated with 10% NaOH to give the free base **732b**. Treatment of **732a** with a mixture of HCl–AcOH resulted in C5-deamination to give **734**, which was obtained directly by the reaction of **718** with thiosemicarbazide hydrochloride in acetic acid. Further heating of **734** in HCl–HOAc effected C8-ester hydrolysis to give **735**, which was also obtained from **732a** under similar reaction conditions. Reaction of **731** with thiosemicarbazide in acetic acid gave **733**, whose heating in HCl–HOAc gave **736**.

Thiation of the triazinoindazolones **737** ($\text{X}=\text{O}$), with phosphorus pentasulfide gave **737** ($\text{X}=\text{S}$), whose reaction with hydrazine gave **738**, which



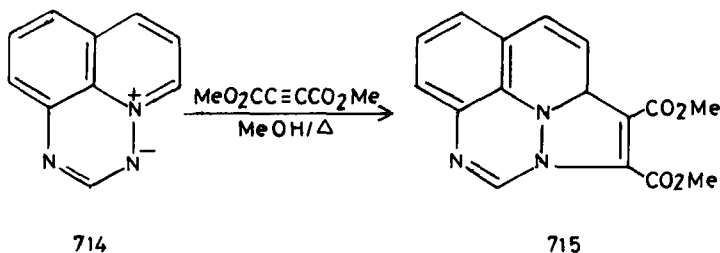
SCHEME 161



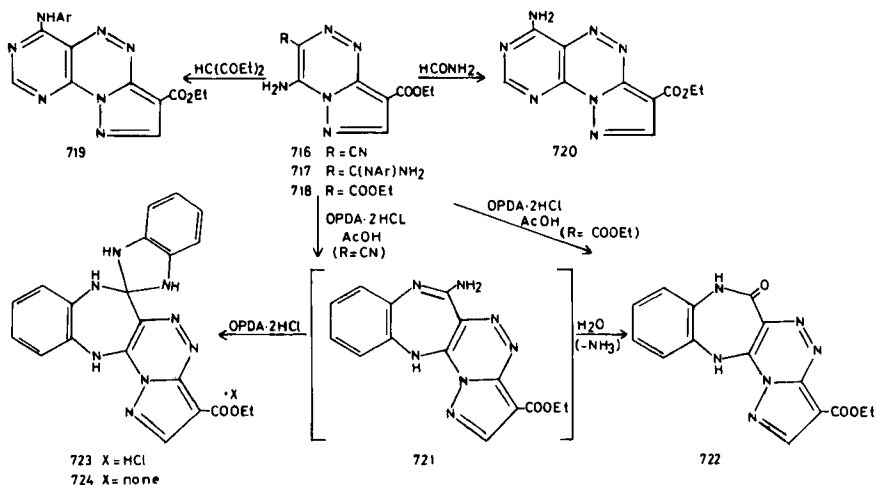
SCHEME 162

cyclized to 1,2,3,4-tetrazolo[5',1':6,1][1,2,4]triazino[4,5-*b*]indazole **739**. Compound **738** underwent cyclization to 3-thioxo-1,2,4-triazolo-[3',4':6,1][1,2,4]triazino[4,5-*b*]indazole **740** (84JHC91), which was alternatively obtained from **741**.

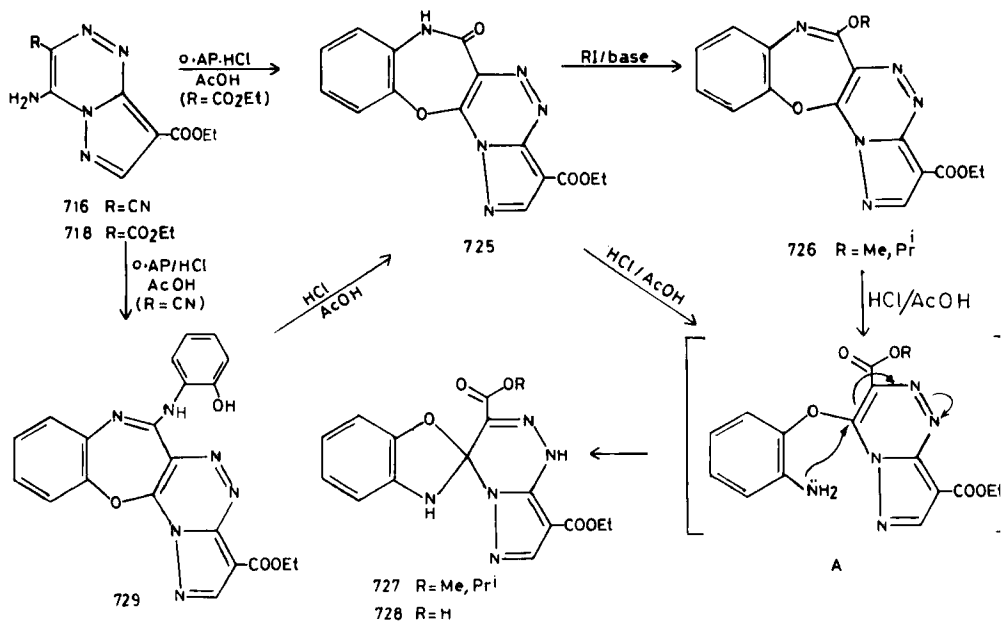
Polycyclic compounds having a pyrazolotriazine ring at the center are used to print polyester, polyamide, acrylic acetate and wool fibers with fast and fluorescent yellow shades (76GEP2527288). They were prepared by coupling diazotized 3-aminoindazole **742** with 2,6-(disubstituted amino)-3-cyano-4-methylpyridine of type **743** to give **744** (74GEP2417916; 75GEP2360986). Similarly, **745** coupled with 2,4,6-tris(diethylamino)pyrimidine **746** in concentrated hydrochloric acid to give **747** (75GEP2355967). 3-Aminoindazole was diazotized to **748** and coupled with 2-phenyl-4,6-



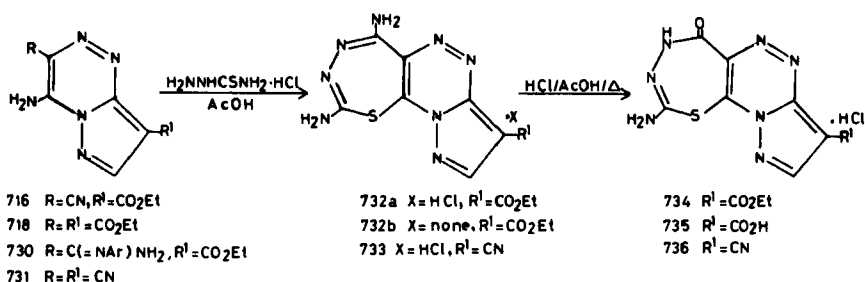
SCHEME 163



SCHEME 164



SCHEME 165



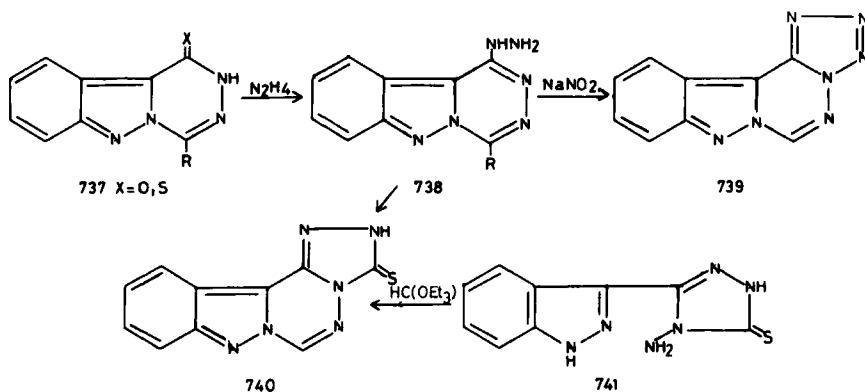
SCHEME 166

disubstituted pyrimidine to give the azo derivative **749**, which was cyclized to **750** (76GEP2430565; 78BRP1502912, 78GEP2707710).

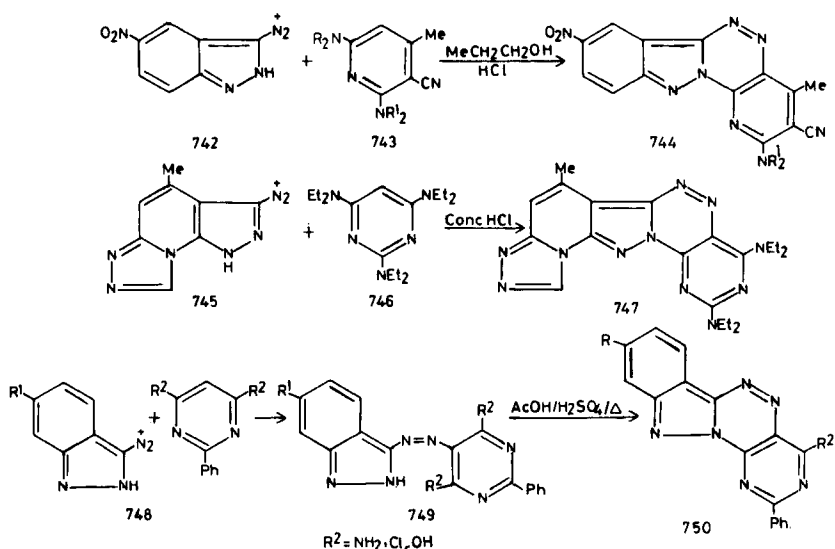
1,2,3,4-Tetrahydropyrimido[4',5':5,6][1,2,4]triazino[4,3-*b*]indazole-2,4-dione **752** was prepared (76CCC3090) by cyclization of compound **751**.

Cyclocondensation of **754** with phenacyl bromide gave (86JHC721) 3-phenyl-7,7,11-trimethyl-8*H*-benzopyrano[4,3-*e*]imidazo[1,2-*b*][1,2,4]-triazine **755**. Cyclization of the 3-hydrazino derivative **756**, with formic acid gave **757**. Compounds **754** and **756** were prepared by reaction of the triazinobenzopyrane **753** with phosphorus oxychloride, followed by amination or hydrazinolysis (86JHC721).

Benzopyrano[4,3-*e*]pyrimido[1,2-*b*][1,2,4]triazines **759** and benzopyrano[3,4-*e*]pyrimido[1,2-*b*][1,2,4]triazines **762** were prepared by reaction of the aminobenzopyranotriazines **758** or **761** with β -keto esters. Catalytic reduction of **759** and **762** afforded the tetrahydro derivatives **760** and **763**, respectively (90JHC1917).



SCHEME 167



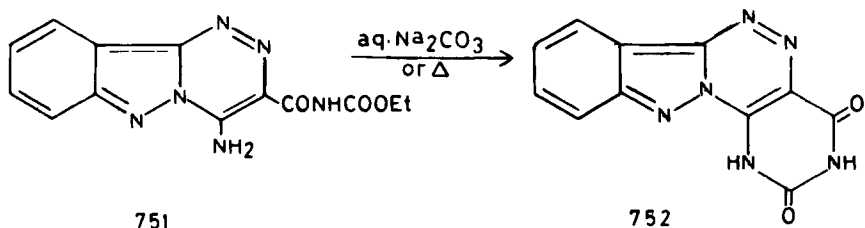
SCHEME 168

Cyclization of the hydrazinotriazinobenzimidazole **764** with carboxylic acids gave [1,2,4]triazolo[3,4:6,1][1,2,4]triazino[4,3-*a*]benzimidazoles **765** (87SC1533).

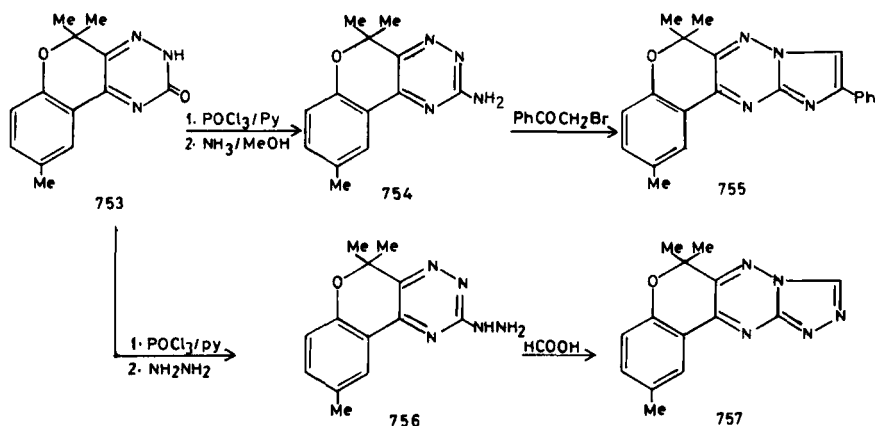
Cyclization of imidazo[4,5-*e*][1,2,4]triazine **766** with bromoacetic acid and aromatic aldehydes (80URP765270) octahydroimidazo[4,5-*e*]-thiazolo[3,2-*b*][1,2,4]triazine-3,7-diones **767**.

Reaction of **768** with one carbon inserting agents, such as formic acid or carbon disulfide, gave (89MI1) **769** and **770**, respectively. Methylation of **770** gave **771**.

Pyrido[2,3-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine-1-oxides **774** were prepared from **772** by reaction with hydrazine, followed by cyclization of the



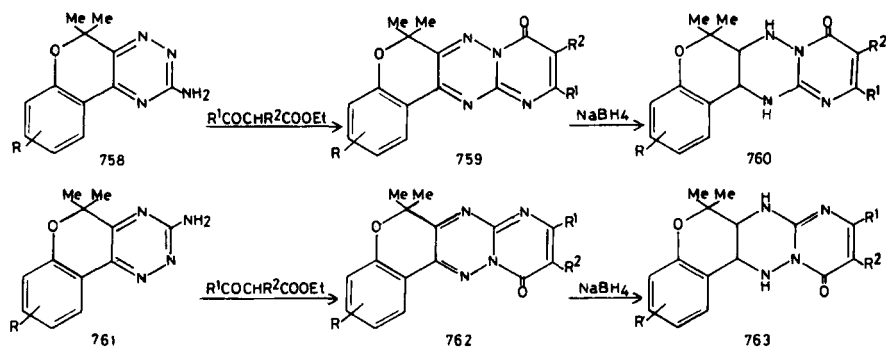
SCHEME 169



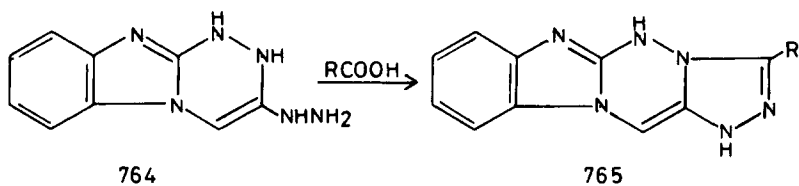
SCHEME 170

hydrazine derivative **773** with *ortho*-esters to give **774**. Reduction of **774** gave **775** (74MI2).

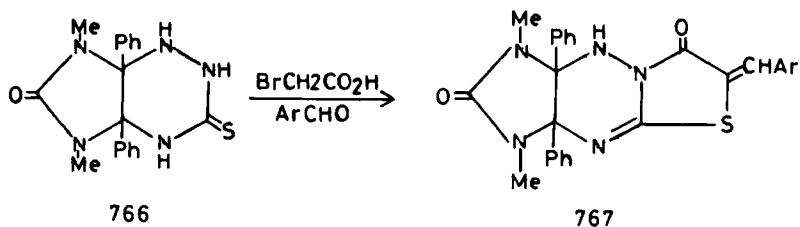
Cyclization of **776** with *ortho*-esters gave (83JOC1628) [1,2,4]triazolo-[4,3-*b*]pyrimido[5,4-*e*][1,2,4]triazines **777**, whereas reaction with sodium nitrite afforded the corresponding tetrazolopyrimidotriazine **778**. 3-Azido-pyrimido[4,5-*e*][1,2,4]triazine **779** exists in a cyclic form as tetrazolo derivative **780**, as shown by X-ray analysis (86KGS114). In solution the position of the $779 \rightleftharpoons 780$ equilibrium depended on temperature and solvent. Higher temperatures favored **779**. Azido compound **779** predominated in water, and tetrazolo compound **780** predominated in pyridine. Addition of sodium azide to the aqueous solution shifted the equilibrium toward **780**. The



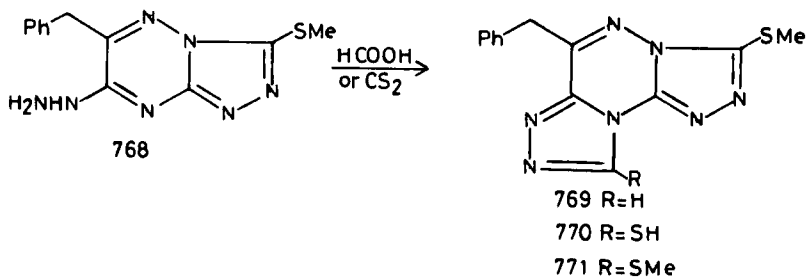
SCHEME 171



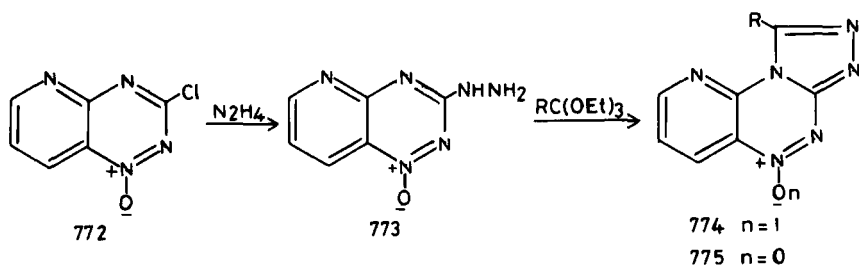
SCHEME 172



SCHEME 173



SCHEME 174



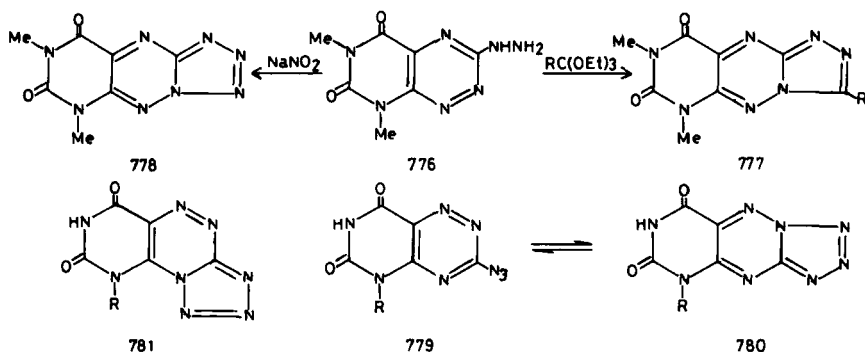
SCHEME 175

mass spectra of a series of azides **779** and tetrazoles given as the angular isomers **781** were studied (83KGS547).

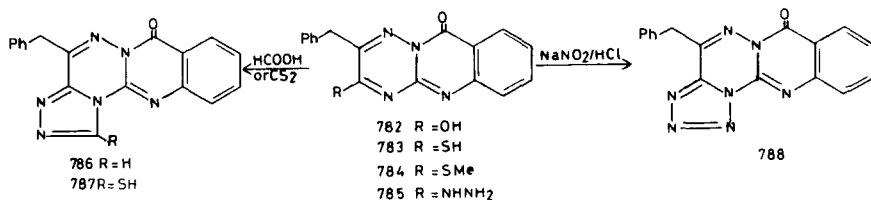
Thiation of [1,2,4]triazino[3,2-*b*]quinazoline-3,10-dione **782** with phosphorus pentasulfide in pyridine proceeded selectively to give the 3-thioxo analogue **783**. The latter was converted to the corresponding 3-methylthio derivative **784** by reaction with methyl iodide. Treatment of **784** with hydrazine gave **785**, which was converted to **786** and **787** by cyclization with formic acid or carbon disulfide (90JHC591). Cyclization of **785** with sodium nitrite in hydrochloric acid gave **788** (90JHC591).

Cyclocondensation of pyrido[2,1-*f*][1,2,4]triazine **789** with phenacyl bromides (84S697) gave **791**, whereas reaction of **790** with isothiocyanates gave **792**.

The zwitterionic pyrido[1,2-*b*]pyridazino[3,4-*e*][1,2,4]triazines **794** and **795** were prepared from furopyridotriazinium salt **793** by reaction with



SCHEME 176



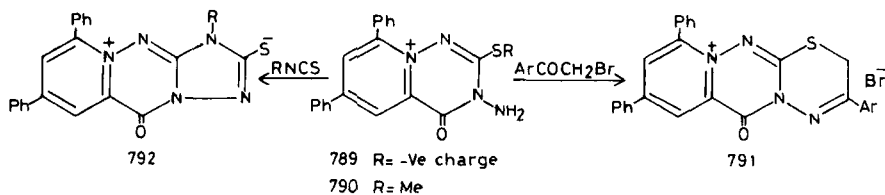
SCHEME 177

either methylhydrazine or 1-acyl-2-methylhydrazine. Similarly, reaction of **793** with 1-formyl-1-methylhydrazine gave **796** via the formation of the hydrazones (89CB1935; 90CB1415). Efforts to synthesize aryl-substituted zwitterions led to simultaneous formation of the analogue of **794** and the pyrazolopyrido[1,2,4]triazine **798** (90CB1415). Reaction of **793** with ammonia gave the pyrido[1,2-*b*]pyrrolo[2,3-*e*][1,2,4]triazine **801** (89CB1935).

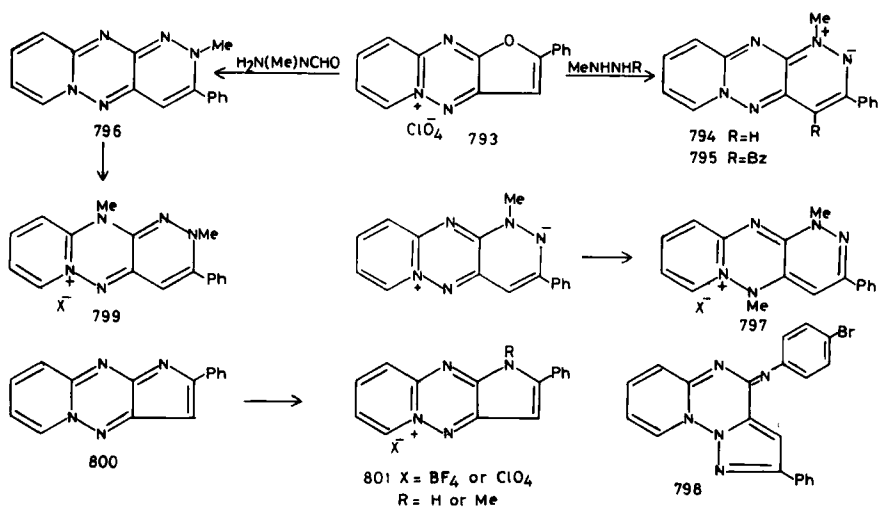
Products **797**, **799**, and **801** were prepared by methylation of the respective precursors. The regiospecific electrophilic attacks are interpreted by a modified application of FMO theory involving a consideration of the in-plane lone pair of the ring nitrogen (91CB1477).

Heating 7,8-diamino-1,3-dimethylxanthine **802** with hydrochloric acid gave azapteridine **803**, which on treatment with alkylamines gave [1,2,4]-triazino[2,3-*f*]purines **804** (87CPB4031).

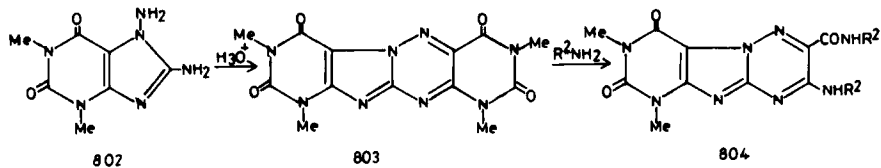
The X-ray structure of pyrazolo[5',1':3,4][1,2,4]triazino[1,6-*a*]indole derivative **805** was obtained (92MI2).



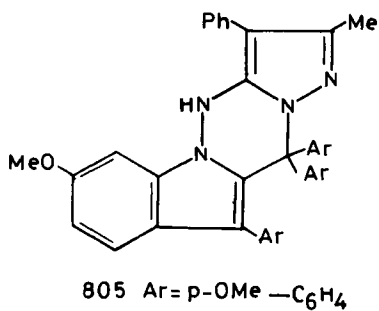
SCHEME 178



SCHEME 179



SCHEME 180



SCHEME 181

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